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MAGELLANIC CLOUDS, X. AN EVALUATION OF THE ZERO POINT CORRECTION

By Harlow Shapley and Virginia McKibben Nail

HARVARD COLLEGE OBSERVATORY

Communicated November 25, 1953

1. In the sixth paper of this series we give the revised total magnitudes of thirteen clusters that on the grounds of spectral class, color, and structure appear to be typically globular and comparable in all respects to the globular clusters of our own galactic system.[1] The revised values support the hypothesis that the zero point of the period-luminosity curve for classical cepheids should be corrected by something like 1.5 magnitudes, and that in consequence the distances of the Clouds are approximately double the values formerly accepted.[2] On the still more reasonable assumption that the globular clusters of our system and of the Andromeda Nebula are structurally the same, with similar luminosity characteristics, Baade has proposed the revision of extragalactic distances, basing his argument in the first place on the failure to resolve easily with the Hale reflector the clusters of the Andromeda galaxy and find in them some stars brighter than the twenty-first magnitude.[3]

But the total magnitudes of globular clusters, used in the sixth paper, are not very satisfactory indicators of distance because of the large spread in the intrinsic luminosities. The apparent magnitudes for the seven clusters in the Large Cloud, for instance, vary from apparent magnitude 9.9 to 11.7. In our galactic system the absolute magnitudes of thirty clusters in high galactic latitudes[4] range approximately from -10 to -5. The apparent magnitudes in the Andromeda Nebula according to Hubble's first analysis[5] range from 15 to 18, a spread confirmed by Seyfert and Nassau.[6] Moreover, the measures of the fuzzy images of clusters are difficult, even for photoelectric photometry; the distribution of the magnitudes is probably not gaussian, and the surveys in all three galaxies may be incomplete for faint globular clusters. The mean and median magnitudes which we used for the Clouds and our Galaxy are therefore incapable of yielding a precise value for the distance revision. A more satisfactory criterion of the distances of galaxies than that provided by the total magnitudes of globular clusters is desirable. Fortunately, at least for the Magellanic Clouds, a better criterion is available.[2]

2. In the early work at Mount Wilson the brightest absolute magnitudes of individual stars in many of the local globular clusters were found to be between -1.0 and -1.5 (photographic), and this result has been verified by several observers. The clusters in the Magellanic Clouds have been difficult to resolve. Their brightest stars (on the formerly accepted distance) should have been easily

photographed at magnitude 16. But they were not, and this absence of bright stars, along with the failure to find RR Lyrae variables in the clusters at the expected magnitudes (17 to 18), cast doubt for some time on the actual comparability of the Magellanic clusters with those of our Galaxy. A similar doubt prevailed with respect to the clusters of M 31. With the revised distances, however, the total magnitudes we find for the clusters in M 31 and the Magellanic Clouds agree satisfactorily with the values for the local globular clusters, and the non-appearance of sixteenth magnitude stars in the Magellanic clusters and the absence from them of RR Lyrae variables at apparent magnitude 17 to 18 are to be expected.

Following the method employed for many of the local globular clusters, we shall use the bright stars in the Magellanic Cloud clusters rather than their variables to determine a new distance modulus and a new correction for the extragalactic distance scale. That is, assuming that the Magellanic Cloud clusters are typically globular, we can measure the apparent magnitudes of their brightest stars, use the

TABLE 1

GLOBULAR CLUSTERS OF THE MAGELLANIC CLOUDS

CLUSTER	DISTANCE	TOTAL MAGNITUDE	SPECTRUM	CLASS	TELESCOPE		MAGNITUDE OF STARS 6	30	25	$m - M$
NGC 121	2°.6	11^m.4	G5	IV	ADH		17^m.7	18^m.4	18^m.01	19^m.34
416	0.9	11.8	K?	IV	SB		17.4	18.4	18.13	19.32
419	0.8	10.4	G	V	ADH		17.4	18.07	17.73	19.01
						Mean	17.52	18.27	17.92	19.20 ±0.08
1783	3.3	10.6	F5:	V	SB		17.15	17.9	17.53	18.81
1806	2.0	11.3	G:	VII	SB		17.9	18.35	18.15	19.34
1835	2.0	10.5	F8	VI	SB		17.8	18.35	18.02	19.29
1846	1.7	11.0	G5	X	SB		17.45	18.25	17.80	18.89
1856	1.6	9.9	G:	V	SB		16.95	17.95	17.50	18.76
1978	2.1	10.7	G	III	ADH		17.15	18.25	17.93	19.15
2056	2.4	11.7	G	IV	ADH		17.25	18.0	17.77	19.00
						Mean	17.35	18.15	17.79	19.01 ±0.06

reduction factors derived for the bright stars in local globular clusters,[7] and compute the distances of the Magellanic Clouds without reference to cepheid variables. For the Magellanic Clouds this bright star method may be more dependable than one based on cluster variables, when they are discovered and measured, since the magnitude standards are safer (and will remain so) at the seventeenth magnitude than at the nineteenth magnitude where the cluster variables should appear.[8]

3. In table 1 we have listed ten of the thirteen clusters which in the sixth paper of this series were accepted as globular; for the others our plate material is insufficient. The first three are associated with the Small Cloud. The magnitudes are based on the standard photographic sequences that we currently use for various studies of variable stars in the two Clouds. The zero points and the scale to magnitude 15.1 for the Small Cloud and 14.6 for the Large are supported by photoelectric work at the Boyden Station.

The plates used for setting up the secondary sequences around each cluster were made with the ADH telescope; Dr. E. M. Lindsay's tabulated distance corrections

were taken into consideration.[9] Since both the secondary sequences and the clusters are in the centers of the reflector plates, no distance corrections were applied to the final magnitudes when the SB series was used. It has been necessary to work away from the centers of the clusters, which are too compact on our plates for useful photometry of individual stars.

Presumably all the ten clusters are actual members of the Magellanic Clouds. We assume that their distances from the observer are equal, although Cloud thickness may contribute an item of $\pm 0^m.2$; in the mean, however, the thickness factor should cancel out.

A number of clusters which appear on first inspection to be globular contain bright stars of the sixteenth magnitude; but on the evidence of color, spectral class, easy resolvability, and absence of RR Lyrae variables at magnitude 17.5, they must be classed as open clusters. For example, NGC 1866 in the Large Cloud has been explored between the fourteenth and eighteenth magnitudes for stellar variation, but only classical cepheids appear;[10] it is therefore removed from the tentative list of globular clusters.

In table 1 the columns contain, for each cluster, after the NGC designation:

Distances in degrees from the geometrical centers of the Clouds
Total magnitudes (from the sixth paper), with double weight given to the photoelectric measures
Spectra (Harvard)
Classes of Cluster
Telescopes used for bright star magnitudes (ADH indicates the Baker-Schmidt instrument, and SB, the Rockefeller reflector)
Magnitudes of sixth and thirtieth stars (in order of decreasing brightness), and mean magnitudes of twenty-five (sixth to thirtieth, inclusive). For NGC 1835, 1856, and 1978, the eleventh and fortieth stars, and mean of thirty (eleventh to fortieth) were substituted, because of the probably significant contribution to the census for them of Cloud field stars in addition to the foreground galactic stars usually allowed for by ignoring the five brightest magnitudes
The last column contains the deduced modulus for each cluster, with double weight assigned to the modulus from the mean of twenty-five (or thirty)

To obtain the modulus for each cluster we used the reduction factors derived for globular clusters of the galactic system which are tabulated for all twelve classes on page 160 of *Star Clusters*.[7] The mean for the Large Cloud of the values in the last column of table 1, with half weight for NGC 1806 and 2056 because of low quality of the plates measured, gives the modulus:

$$m - M = 19.01 \pm 0.06 \text{ m.e.}$$

For the Small Cloud the material is not sufficient to give a dependable value, but with half weight for NGC 416, which is not well located on the available plates, the mean is 19.20.

4. The classes assigned these globular clusters, which are faint and small, in the Magellanic Clouds cannot be precise, and perhaps they are not closely comparable with those used for the construction of the reduction table in *Star Clusters*. We can completely ignore the classes, however, and compute directly a mean modulus, using the data of table 2, which is constructed in the following manner. For all the globular clusters of our Galaxy that have an appreciable number of RR Lyrae type variables and for which the magnitudes of the bright stars as well as the variables have been measured, we tabulate the magnitude differences: variables (mean

median) *minus* sixth, *minus* thirtieth, *minus* mean of twenty-five. The data are taken from Appendix A of Harvard Monograph No. 2.[11] The weights in the third column of table 2 are based on the number of variables and the qualities of the

TABLE 2

GLOBULAR CLUSTERS OF THE GALACTIC SYSTEM

CLUSTER	CLASS	WEIGHT	$V-6$	$V-30$	$V-\overline{25}$
NGC 362	III	2	2.00	0.70	1.38
3201	X	2	1.22	0.72	1.00
4590	X	5	1.59	0.82	1.10
5139	VIII	3	1.77	1.27	1.46
5272	VI	7	1.58	1.05	1.27
5904	V	7	1.52	0.99	1.29
6205	V	3	1.75	1.28	1.45
6656	VII	4	1.26	0.80	1.13
6723	VII	4	1.63	0.53	1.13
6981	IX	7	1.27	0.60	0.94
7006	I	4	1.97	1.07	1.46
7078	IV	6	1.50	1.08	1.32
7089	II	3	1.46	0.95	1.10
Mean			1.58	0.91	1.23
			±0.07	±0.07	±0.05
Weighted mean			1.55	0.91	1.22

observations involved. The inclusion in the table of data from more recent research on the numbers of variables or their magnitudes would not sensibly affect the results, which depend only on magnitude differences and not on photometric zero points. The reduction factors (unweighted) are given at the bottom of the table with their mean errors; also the weighted means. By combining the latter with the corresponding mean apparent magnitudes for the Large Cloud (table 1), we have:

	SIXTH	THIRTIETH	MEAN OF 25
Apparent magnitude	17.35	18.15	17.79
Absolute magnitude	−1.55	−0.91	−1.22
Modulus	18.90	19.06	19.01

The weighted result is $m - M = 19.00$. Similarly computed, the modulus for the Small Cloud is $m - M = 19.13$, but again we note that this is a preliminary value. As matters stand we have no convincing evidence that the distances of the two Clouds differ by more than the uncertainty of the determinations.

5. *Conclusions.*—(*a*) The apparent photographic magnitudes of the brightest stars in the Magellanic globular clusters, when compared with analogous material for the globular clusters of the galactic system, give us a better evaluation of the zero point of the period-luminosity curve for clasical cepheids in the Magellanic Clouds, and a better measure of the distances, than can be obtained from their variable stars, or from the total magnitudes of their clusters, or from their novae.

(*b*) For the large Cloud from data derived for seven clusters we obtain the distance modulus $m - M = 19.0$, uncorrected for space absorption. The value of the modulus, with regard given to cluster class, is 19.01; and without regard to cluster class, 19.00.

(*c*) With less weight the values for the Small Cloud are, respectively, 19.16, 19.20, and 19.13.

(*d*) Taking $0^m.4$ as the space absorption for the Large Cloud, we get the revised distance of 170,000 light years, and a correction factor for distances on the old scale of 2.1. The uncertainty in this factor, ± 0.1, does not include undetected systematic errors in the magnitude sequences. Such errors will be reduced, and this correction corrected, when further faint photometry has been done in the Magellanic Clouds.

[1] These PROCEEDINGS, **39**, 349–357 (1953); *Harvard Reprint* 372.

[2] Paper presented at the Meeting of the American Astronomical Society, Boulder, Colo., August, 1953.

[3] Baade, W., Report at International Astronomical Union Meeting in Rome, 1952.

[4] These PROCEEDINGS, **30**, 61–68 (1944); *Harvard Reprint* 257.

[5] Hubble, E. P., *Mt. Wilson Contr.* 452 (1932).

[6] Seyfert, C. K., and Nassau, J. J., *Ap. J.*, **102**, 377–381 (1945).

[7] *Harvard Monograph* **2**, Table XI, II, 160 (1930).

[8] Thackeray and Wesselink working with the Pretoria reflector have announced the finding of such variables in three Magellanic Cloud clusters (Thackeray, A. D., and Wesselink, A. J., *Nature*, **171**, 693 (1953)).

[9] Lindsay, E. M., *Irish Ast. J.*, **2**, 143 (1953).

[10] *Ast. J.*, **55**, 249–251 (1951); *Harvard Reprint*, Series II, 36.

[11] *Harvard Monograph* **2**, Appendix A, 224–227 (1930).

INACTIVATION AND REACTIVATION OF B. MEGATHERIUM PHAGE

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Communicated December 18, 1953

Megatherium phage is completely inactivated by distilled water or very dilute salt solutions. Phage inactivated in this way may be completely reactivated by suspending it in concentrated solutions of sodium acetate or in slightly acid peptone solutions. This "reversibly inactivated" phage is quite stable in neutral peptone solutions but gradually changes over to an irreversibly inactive form.

The reversible inactivation occurs in the range of pH 4.5–7.0, and 0°–25°, in very dilute salt solutions. Above pH 7.0 no inactivation occurs; below pH 4.5 the inactivation is irreversible.

The inactivation is prevented by .05 molar monovalent cations or 1×10^{-4} molar bivalent cations. Five γ peptone/ml. also prevents inactivation.

Air in the laboratory and N_2 or O_2 from commercial tanks contain traces of some impurity, probably a volatile base, which also prevents inactivation, since, if large volumes of the gases are bubbled through distilled water, the solution no longer causes inactivation of the phage. Carefully purified gases have no effect.

The "reversibly inactivated" phage may be reactivated by standing in peptone solution adjusted to pH 5.0; 0.5 to 2.0 *M* Na Acetate; 1×10^{-3} to 1×10^{-4} *M* Na_2HCO_3 or Na_2HPO_4. A suspension of heat-killed *B. megatherium* sensitive, which has been washed repeatedly in distilled water, also reactivates, as does the supernatant solution from such a suspension.

Neither the inactivation nor the reactivation is affected by diffuse daylight. The method used to dilute the phage suspension or to add the concentrated phage to the distilled water does not affect the results.

The reversible inactivation is not due to precipitation or aggregation of the phage since reversibly inactivated phage centrifuges down at the same rate and to the same extent as does the active phage. (The loss of activity is so great that, to explain the results on this basis, it is necessary to assume the existence of clumps or precipitated particles containing at least 1000 active phage particles.) Gentle stirring does not affect the rate of inactivation or reactivation; violent stirring inactivates permanently.

The inactivation in the distilled water is not due to adsorption of the virus on the glass, since alternate samples from the same pipette are active, if added to pH 5.0 peptone, but inactive if added to pH 7.0 peptone. The inactivity of the pH 7.0 peptone solution cannot be due to adsorption on the glass either, because a sample of the inactive solution, removed to another tube and then titrated to pH 5.0, becomes active.

The reversibly inactivated virus becomes permanently inactivated on standing in peptone more rapidly than does the active virus. The inactivation may therefore follow this course: active virus$\rightleftharpoons$reversibly inactive$\rightarrow$inactive.

Reversibly inactivated virus is absorbed by sensitive cells to about the same extent as active virus.

No difference has been found between reactivated virus and the original active virus.

These results were obtained with megatherium "T" phage, but preliminary experiments indicate that megatherium "C" phage[1] reacts in the same way. The reaction is very similar to the reversible denaturation of trypsin.[2] The reversible inactivation of a staphylococcus phage has been previously reported by Krueger and Mundell.[3]

[1] Gratia, A., *Compt. rend. Soc. Biol.*, **123**, 1018 (1936).
[2] Kunitz, M., and Northrop, J. H., *J. Gen. Physiol.*, **17**, 591 (1934).
[3] Krueger, A. P., and Mundell, J. H., *Proc. Soc. Exp. Biol. and Med.*, **34**, 410 (1936).

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*SOME PHYSICAL CHEMICAL EXPERIMENTS WITH HEMOGLOBINS FROM NORMAL AND GENETICALLY ANEMIC MICE**

By S. J. Singer and Elizabeth S. Russell

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Communicated by C. C. Little, November 30, 1953

Among several inherited blood dyscrasias described for the mouse is a particularly interesting series of macrocytic anemias appearing in affected animals before birth and persisting throughout life.[5, 14] These anemias result from the action of the dominant deleterious genes of the *W*-series (*W*, W^v, *w*), which also condition abnormalities in pigmentation and germ-cell development.[13, 15] Four of the six genotypes possible for this locus have significantly reduced red-cell counts and

increased mean cell diameters, the severity of the anemia depending on the genotype. The most severely affected, WW, with one-seventh to one-fifth of the normal erythrocyte number, is lethal at, or shortly after, birth; WW^v, with one-third to one-half the normal number, is semiviable, many individuals dying before one month of age; W^vW^v, with one-half to two-thirds the normal count, is viable but especially susceptible to intercurrent infections; and W^vw, with seven-eights the normal count, is a healthy individual. Physiological experimentation[4] has shown that W^vW^v and WW^v individuals respond to bleeding and low barometric pressure by forming new erythrocytes, but fail to respond to treatment with iron or liver extract, or more recently[2] to folic acid or B-12 therapy. Study of the chemopathology of hemoglobin synthesis in W^vW^v anemic animals, with α-C^{14} glycine injected into normal and anemic littermates,[1] shows delay of α-C^{14} incorporation into protoporphyrin, but no delay in its incorporation into globin, and suggests that "one of the biochemical lesions resulting from the W^v mutation is localized in the chain of events leading to the synthesis of protoporphyrin from glycine." These tracer experiments also demonstrated the same erythrocyte life-span in normal and W^vW^v anemic mice.

Recently, investigations of blood from normal adult humans and from individuals suffering from several different types of hereditary anemias have demonstrated that considerable differences exist in the physical chemical properties of the hemoglobins present in the normals and in each of the anemic types. In sickle-cell anemia[11, 16, 6, 7] a small difference in the structure of the globin portion of the hemoglobin molecule is believed to lead directly to pathological behavior (sickling) and subsequent destruction of the red-cells. In Cooley's anemia, or Thalassemia major, characterized by "target" cells, a considerable portion of the hemoglobin appears to be electrophoretically indistinguishable from human fetal hemoglobin.[11, 12] It is suggested that Cooley's gene "block(s) the production of normal adult hemoglobin (and) causes the continued production of fetal hemoglobin (as a) compensatory response."[12] In addition, two other types of abnormal human hemoglobin have been described[8] which differ in physical chemical properties from normal and sickle-cell anemia hemoglobins, and which are associated with diseases similar to sickle-cell anemia.

In view of these findings, some experiments were performed with the hemoglobins of normal and W-anemic mice to explore the possibility of physical chemical differences among these molecules.

The animals used in these experiments, raised in the Jackson Laboratory, were offspring of W^vw parents isogenic with the C57BL/6Jax inbred strain, and thus were genetically identical except for the W-locus. Fifteen sets of adult W^vW^v, W^vw, and ww littermates, where possible of the same sex (predominantly male), were accumulated to provide the volume of blood necessary for these experiments. At the time of sacrifice, the animals ranged from $2^1/_2$ to 9 months of age, necessarily with the same distribution of ages in each genotypic group. Using sterile methods, blood was collected from the exposed ventricle with a Luer syringe and No. 27 gauge needle. Blood from all animals of the same genotype was pooled (10.3 ml. from W^vW^v, 11.0 ml. from W^vw, and 10.2 ml. from ww) and diluted with an equal volume of Alsever's solution[9] to prevent clotting.

The hemoglobins were prepared from the different blood samples by a method

similar to that of Drabkin,[3] but were not crystallized. The blood samples were centrifuged, and the supernatants removed from the pellets. The pellets were suspended in cold 0.9% NaCl and centrifuged and washed three times. After the last centrifugation, 2.0 ml. distilled water and 1.0 ml. toluene were added to each pellet, carbon monoxide was bubbled through the suspension, and the cells were allowed to lyse overnight at 4°C. The laked cell suspensions were then centrifuged and the clear red aqueous layers drawn off by syringe. These concentrated stock solutions were stored at 4°C.

Because of the limited supply of blood, a complete electrophoretic study of the hemoglobins was not feasible. Instead, one set of conditions was chosen to permit a sensitive test for electrophoretic differences among the hemoglobins. Solutions of carbonmonoxyhemoglobin (CO-Hb) at a concentration of 5.0 mg./ml. were prepared by diluting the concentrated stock solutions with cacodylate-NaCl buffer pH 6.69, ionic strength 0.05, containing 0.03 *M* NaCl. The solutions were then

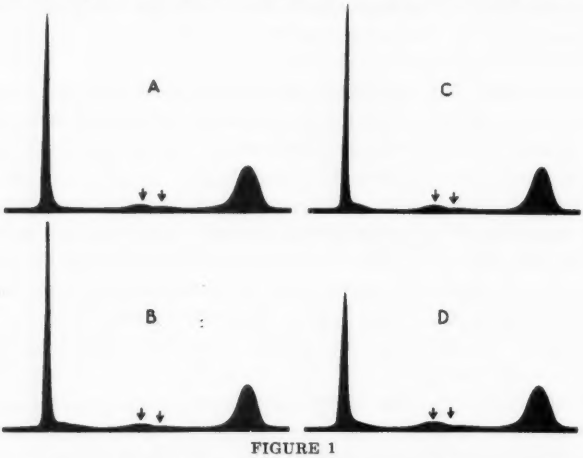

FIGURE 1

Longsworth scanning electrophoresis diagrams of mouse carbonmonoxyhemoglobins from the following genotypes: (A) *ww;* (B) $W^{v}w$; (C) $W^{v}W^{v}$. (D) is an equal part mixture of A and C. In each diagram, the left side of the pattern is the ascending, and the right, the descending diagram. The starting positions in the two limbs are indicated by the arrows. The electrophoretic conditions are given in the text.

dialyzed overnight at 4°C. against the same buffer saturated with carbon monoxide. Electrophoresis was performed in a Klett Tiselius apparatus at 2°C., at a field strength of 8.1 volts/cm. for 12,000 seconds. A tungsten filament light source was used.

Four experiments were performed, on hemoglobins from *ww*, $W^{v}w$, and $W^{v}W^{v}$ mice, and on an equal part mixture of the first and third. The electrophoretic patterns are essentially identical, as is evident in figure 1, as are the mobilities listed in table 1.

In addition, sedimentation experiments were performed in a Spinco analytical ultracentrifuge with CO-Hb from *ww* and $W^{v}W^{v}$ mice. The solutions were the

same as those examined electrophoretically. The same value for the sedimentation constant, $s^{w}_{20} = 4.3S$, was obtained, at a rotor speed of 59,780 r. p. m.

Preliminary solubility measurements in phosphate buffer, pH 7.1, ionic strength 4.0, indicated further that the CO-Hb from *ww* and $W^{v}W^{v}$ mice have about the same solubility, 0.4 mg./ml.

The conditions utilized in the electrophoresis experiments described are those under which sickle-cell anemia CO-Hb and normal human adult CO-Hb are readily distinguishable.[16] A difference of only two to four electric charges on the molecules can account for the difference in their electrophoretic properties.[11] Therefore, the electrophoretic data presented in this paper, together with the ultracentrifugal and solubility results, indicate that the hemoglobins of *ww*, $W^{v}w$, and $W^{v}W^{v}$ mice are very similar, if not identical. It is of course possible that subtle differences

TABLE I

ELECTROPHORETIC MOBILITIES

MOUSE GENOTYPE	MOBILITY × 10^5 CM.^{2}/SEC /VOLT ASCENDING	DESCENDING
ww	+3.53	+3.28
$W^{v}w$	3.49	3.31
$W^{v}W^{v}$	3.53	3.32
ww + $W^{v}W^{v}$	3.60	3.32

among the hemoglobins exist which are not detectable by the means utilized in this study, and that other techniques might reveal them. However, on the basis of our results, we suggest tentatively that the physical chemical properties of the hemoglobins of normal and *W*-anemic mice are sufficiently similar to exclude these properties as primary factors in the causation of the anemias. This is consistent with the previous studies mentioned earlier, which show that the $W^{v}W^{v}$ anemia is one of arrested cell-maturation, with a normal life-span of the erythrocytes in the circulation. This is a very different etiology from those of the hereditary human hemolytic anemias, in which excessive hemolysis and reduced life-span of the erythrocytes are involved.

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† Contribution No. 1199.

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*THE LUMINESCENT OXIDATION OF REDUCED RIBOFLAVIN OR REDUCED RIBOFLAVIN PHOSPHATE IN THE BACTERIAL LUCIFERIN-LUCIFERASE REACTION**

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Communicated December 11, 1953

Numerous earlier studies on various light-producing species have suggested a relation between luminescence and flavin compounds,[1-8] although it has not been demonstrated heretofore that the enzymatic oxidation of reduced flavins by luminous bacterial extracts will result in luminescence. From the similar kinetics of light emission when either flavin mononucleotide (FMN = riboflavin phosphate) or reduced diphosphopyridin nucleotide ($DPNH_2$ = reduced coenzyme I) was the last factor added to luminous bacterial extracts,[9] it seemed probable that the sole function of $DPNH_2$ in luminescence was to produce reduced flavin, and, further, that reduced flavin might be considered as bacterial luciferin. Because of technical difficulties in handling reduced flavins these compounds were not used in earlier studies on the extracted cell-free luminescent system from bacteria. We can now report that either reduced riboflavin or reduced flavin mononucleotide will support the luminescence of *Achromobacter fischeri* extracts in the absence of added $DPNH_2$.

For the experiments reported here *Achromobacter fischeri* was grown and 5 per cent extracts prepared according to the method of Strehler and Cormier.[5,10] Riboflavin and flavin mononucleotide were obtained from Merck and Company and Sigma Chemical Company, respectively, and were used in concentrations of about 100 μg./ml. These compounds were reduced in a stream of catalytically purified hydrogen in the presence of platinized asbestos. For visual qualitative experiments the 2-chamber "A tubes" described earlier[11] were used (modified to filter off the platinized asbestos). When the reduced flavin compounds, filtered free of platinized asbestos, were mixed anaerobically with the enzyme through which hydrogen had been passed, a dim flash of luminescence (probably due to traces of oxygen) occurred, which soon disappeared. However, on aerating the tube, a bright light of about 20 seconds duration appeared.[13]

Quantitative light determinations were made and the time course of the reaction studied with a simple rapid mixing stop-flow method. Light output was measured with a 1P21 photomultiplier under DC operation, and recorded photographically from a cathode ray oscillograph. The flavin compounds employed for the quantitative experiments were reduced in a stoppered centrifuge tube and removed from the tube with a 1-ml. hypodermic syringe after centrifuging down the catalyst. Figure 1 contains photographic oscilloscope tracings of the time course of luminescence

when reduced riboflavin and reduced flavin mononucleotide were added rapidly to the enzyme in the presence and absence of decaldehyde (10 μg./ml).[12] A much weaker luminescence appeared without decaldehyde. Plots of the complete kinetic curves indicate a more rapid rise and a more rapid decay of luminescence in the presence of decaldehyde for both reduced riboflavin and reduced flavin mononucleotide oxidation.

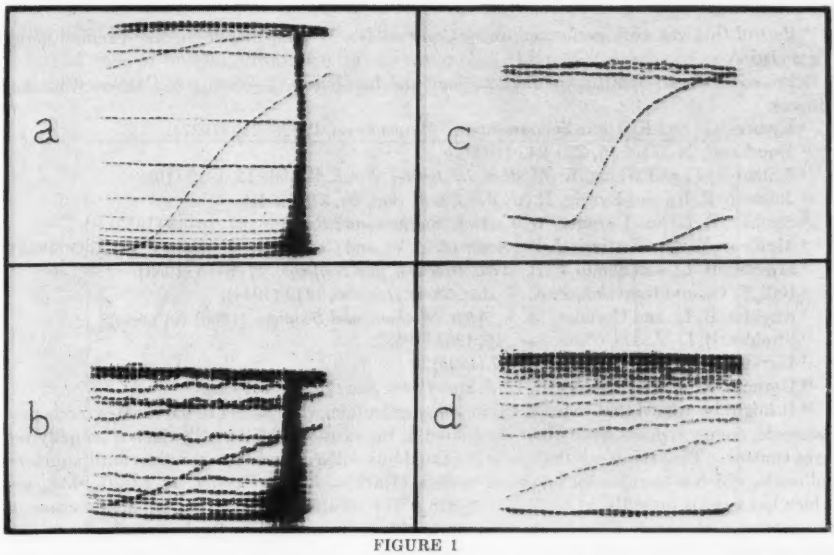

FIGURE 1

Photograph of oscilloscope tracings showing time course of intensity of luminescence (vertical) vs. time (horizontal) when reduced flavin mononucleotide ($FMNH_2$) or reduced riboflavin (RFH_2) are added to bacterial extracts (enzyme) in the presence and absence of decaldehyde. Sweep 0.4 sec.

Approximately 5 mg./50 ml. of riboflavin or FMN were reduced with H_2 + platinized asbestos, 0.2 ml. drawn into a syringe and mixed rapidly with 0.2 ml. of a 5 per cent cell-free aqueous extract of luminous bacterial powders (centrifuged).

(*a*) RFH_2 + (enzyme + 50 μg. decaldehyde), sensitivity (relative) of light-measuring equipment = 0.6; "$^1/_2$ rise time" = 0.20 sec.

(*b*) RFH_2 + enzyme; relative sensitivity 19; "$^1/_2$ rise time" = 0.27 sec.

(*c*) $FMNH_2$ + (enzyme + 50 μg. decaldehyde); relative sensitivity, 2; "$^1/_2$ rise time" = 0.075 sec.

(*d*) $FMNH_2$ + enzyme; relative sensitivity, 8; "$^1/_2$ rise time" = 0.41 sec.

In (*a*) and (*b*) the horizontal lines represent decay of luminescence obtained by triggering the sweep every 5 seconds in (*a*) and every 10 seconds in (*b*) after the maximum of luminescence intensity was reached.

It has been observed[5, 6] that the presence of oxidized riboflavin actually inhibits the luminescence of bacterial extracts when $DPNH_2$ is added. This inhibitory effect of riboflavin on bacterial extract luminescence is probably due to its competitive interaction with flavin mononucleotide at the site of the latter's reduction, rather than in the light-emitting step. It also seems likely that reduced flavin mononucleotide enters closely into the light-emitting reaction, since the "1/2 rise-

time" is of the same order of magnitude as the rate of increase of luminescence when oxygen and long-chain aldehydes are added. That the strong light-quenching effects of dilution of the bacterial extracts may be due to the competition of non-enzymatic auto-oxidation of flavin also seems to be indicated. Finally, in view of the above findings and the well-known fact that flavin compounds are fluorescent and can be made chemiluminescent,[7] it would seem likely that bacterial luciferin is reduced flavin mononucleotide.

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[13] It might be argued that reduced flavin mononucleotide, when added to bacterial extracts plus aldehyde, merely reduces some other compound in the extract ("luciferin") which is actually the light emittor. That this is not the case is indicated by adding reduced 2,6-disodium anthraquinone sulfonate, which is harmless for luminous bacteria (Harvey, *J. Gen. Physiol.*, **13**, 13–20, 1929), and which has a redox potential at pH 7 = − 0.220. The addition does not result in luminescence of the extract. However, when flavin mononucleotide is first added to the bacterial extract plus palmitaldehyde, followed by the reduced anthraquinone, a bright luminescence appears when the mixture is aerated. It has also been determined that when reduced lumichrome (kindly supplied by Dr. R. T. Major of Merck and Company, Inc., Rahway, New Jersey) is added to bacterial extracts plus aldehyde, no luminescence or an extremely faint luminescence is to be observed.

*THE INFRARED ASSOCIATION SPECTRA OF AMIDES IN SOLUTION AND THEIR RELATION TO THE SPECTRA OF POLYPEPTIDES**

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The infrared spectra of amides in solution have been the subject of several previous investigations.[1] Nevertheless, in connection with a systematic study of peptides and related substances, it has seemed desirable to make a quantitative reinvestigation of some of these spectra with the greatly improved instrumental facilities now available. The grating spectrometer employed was used under conditions such that water vapor lines separated by 3 cm.$^{-1}$ were well resolved so that no correction need be made for slit width in intensity measurements. Great precautions were taken in stray light corrections.

In carbon tetrachloride solution acetamide, propionamide, and butyramide exhibit virtually identical spectra in the N—H valence region, from 3100 to 3600 cm.$^{-1}$. A typical example is shown in figure 1. Seven components are distinguishable, the detailed explanation of which will be given in another place. Two of these M_1, and M_2, with width about 20 cm.$^{-1}$ at half peak intensity, are attributable to the monomer, the remainder to associated molecules. The major polymer band, P_1, undoubtedly to be attributed to hydrogen bonded N—H, is very broad and intense with maximum at about 3172 cm.$^{-1}$.

In the case of propionamide we have shown that the five polymer bands maintain constant relative intensities within the entire available concentration range. This

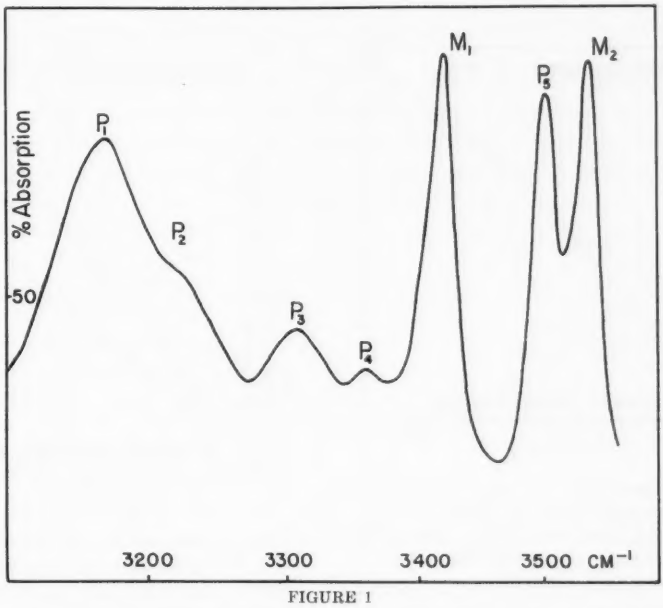

FIGURE 1

The infrared spectrum of propionamide in CCl_4 solution in the 3μ region. Path length 2 cm; concentration approximately 0.004F.

strongly suggests the presence of only one polymer species. A quantitative consideration of the dependence of intensity on concentration showed that polymers higher than the dimer can make only a small contribution at the highest concentrations, and a completely satisfactory fit to the data is obtained on the assumption of simple dimerization. This may be seen in figure 2, where the curve corresponds to an association constant, $K_2 = 46.5$ moles^{-1} liter.

The structure of the spectrum and the intensity measurements lead to definite conclusions regarding the structure of the dimer. In figure 3 it is shown that with increasing concentration the intensities of the dimer bands increase with the squares of the intensities of the narrow bands, M_1 and M_2. Evidently the latter bands are due exclusively to monomer; the dimer has no free NH_2 end-group. The extreme

narrowness of the polymer band P_5 indicates that it is due to the vibration of N—H not involved in a hydrogen bond. Its frequency is in the range to be expected for the "free" hydrogen of an NH_2 group of which the second hydrogen is engaged in such a bond. Since the dimer has no NH_2 end-group it is difficult to imagine that it has only one such hydrogen, and the intensity of P_5 qualitatively supports the belief that there are two. However, one of the two vibrations involving these two atoms appears to be inactive since P_5 shows no evidence of splitting, but on the contrary is quite as narrow as the dimer bands.

This evidence, together with the dissociation energy mentioned below, makes it difficult to escape from the conclusion that the dimer is cyclic with an eight-membered ring closed by two hydrogen bonds. If the amide group is planar as now

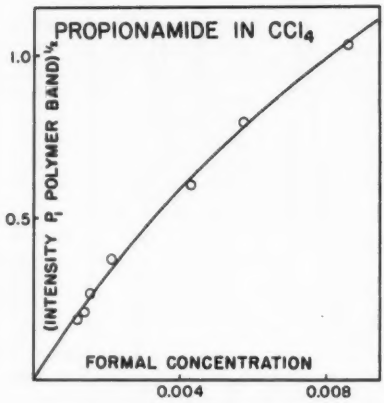

FIGURE 2

Plot of the square root of the optical density at the maximum of the P_1 band, versus concentration (path = 2.54 cm.). The curve corresponds to an association constant K_2 = 46.5 moles^{-1} liter.

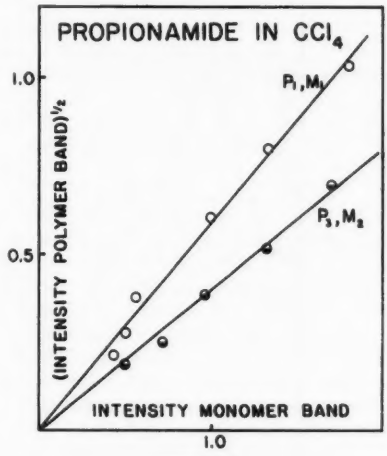

FIGURE 3

Plots of the square root of the optical density at the maximum of a polymer band versus optical density at maximum of monomer band at several concentrations.

seems to be generally admitted, it almost certainly follows from the above that the dimer ring is also planar. The same eight-membered ring configuration closed by two hydrogen bonds has been found in crystalline diketopiperazine[2] and cyanuric acid.[3, 4]

The association energy of the dimer of propionamide has been estimated from the temperature coefficient of the peak intensity of the dimer band P_1. Measurements were made at three temperatures and at two concentrations in a 0.5-inch cell. Figure 4 shows, in effect, plots of log K_2 versus $1/T$. In actual fact the ordinate of a point on the plot is the reciprocal of the concentration which would be required at 25° to give the same degree of association as that observed at T. These reciprocal concentrations are obviously proportional to K_2. They were estimated from a smoothed plot of the experimental data at 25°.

The best value for the enthalpy of association was found to be $\Delta H = -7850 \pm 220$ cal. mole^{-1}, or -3925 ± 110 cal. per hydrogen bond. The best value for the association constant at approximately 25° is $K_2 = 45 \pm 6$ moles^{-1} liter which corresponds to $\Delta F = -2250 \pm 80$ cal. mole^{-1}.

In the ring structures joined by two hydrogen bonds mentioned above, the N—H and C=O bonds of a given molecule are *cis* with respect to each other. This *cis* arrangement has, until now, not been demonstrated to exist in any peptide but it has perhaps not been entirely clear whether its absence is due to packing or other steric requirements or to an inherent lower stability than that of the trans configuration. It therefore seemed worth while to investigate whether N-methyl formamide is able to associate in the same fashion as the unsubstituted amides, since in this molecule steric interference should be at a minimum. There is no very obvious reason why the dimers of the isomeric acetamide and N-methyl formamide should not be quite similar; in fact they are quite unlike.

The heavier substituted amides evidently associate in quite a different fashion from the unsubstituted compounds. A representative spectrum is shown in the lower part of figure 5. At lower concentrations absorption at 3172 cm.$^{-1}$ is negligible, though in addition to the monomer band at 3460 cm.$^{-1}$ a strong absorption centered at 3360 cm.$^{-1}$ gives evidence of polymer, presumably the dimer. With increasing concentration a succession of new components, evidently due to higher polymers, make their appearance at progressively lower frequencies. This decrease in frequency suggests that the hydrogen bond is stabilized as the size of the polymer increases. At an intermediate concentration the maximum of absorption is at the frequency generally characteristic of dipeptides and polypeptides. From this it is reasonable to conclude that the monomer units are linked in chains in a fashion similar to that in which the peptide groups are linked in crystalline α-diglycine.[7] This is supported by dielectric constant measurements made on several substituted amides which have shown the presence of chain polymers.[8, 9]

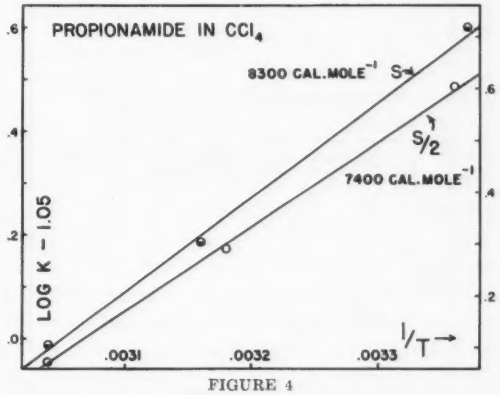

FIGURE 4

Plots of log K_2 versus reciprocal temperature. The symbols S and $S/2$ refer to solutions which were saturated, or half saturated at 18°.

A broad absorption at about 3090 cm.$^{-1}$ is particularly interesting since it appears to correspond to a minor absorption commonly found in the spectra of polypeptides, where it has sometimes been described as an N—H frequency. This interpretation appears very unlikely since this band makes its appearance at the earliest stages of association. An alternative explanation will be discussed in another place.

The available concentration range for N-methyl formamide is limited by its moderate solubility, but in the N—H region its spectrum seems to be entirely

similar to those of higher substituted amides. One is consequently led to the conclusion that even in this case the cis form of the molecule does not exist and that each trans monomer is stabilized by an amount very considerably in excess of half the gain which would result from the formation of a second hydrogen bond in closing the dimer ring.

It is of some interest that the N—H frequency of the dimers of the unsubstituted amides is approximately 160 cm.$^{-1}$ lower than is found in those of the N-substituted compounds. We believe that this is not to be attributed to a difference between cis and trans configurations, but is rather a consequence of the eight-membered ring structure discussed above. Similar differences are found in the crystalline cyclic amides where the cis arrangement exists of necessity. In cyanuric acid two-thirds

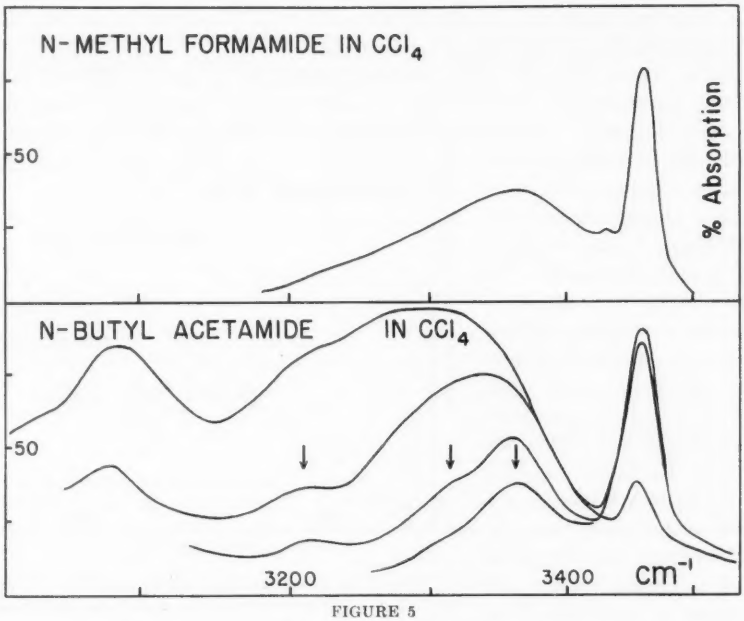

FIGURE 5

The spectra of two N-substituted amides in the 3μ region.

of the hydrogen bonds close eight-membered rings and the corresponding N—H frequency is 3060 cm.$^{-1}$. The frequency of the remaining N—H groups is 150 cm.$^{-1}$ higher.[6] In diketopiperazine where all N—H groups are included in rings the N—H absorption is centered slightly above 3000 cm.$^{-1}$,[5] while in parabanic acid where such rings are absent, it lies around 3200 cm.$^{-1}$.[10] The very low N—H frequency in all these three compounds is possibly the result of stabilization by the many resonating structures which contribute to the ground state of the crystal.

At present there seems little evidence for believing that a cis arrangement of N—H and C=O bonds will necessarily result in a low N—H frequency.

* Contribution No. 1859 from the Gates and Crellin Laboratories. The investigations reported were supported by the Office of Naval Research under Contract N 6-ori-102, VI.

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THE SOLUBILITY OF HYDROCARBONS IN WATER

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Hildebrand[1] has introduced the internal pressure of the liquid phase as a semi-empirical criterion for mutual solubility. Recently one of us has measured the apparent molal volumes of benzene in water solution and it now appears that quantitative expression can be given to the role of internal pressure as a factor affecting solubility. Before discussing the case of benzene it is desirable to review the facts regarding the solubility of the hydrocarbons in water.

1. The solubilities are infinitesimal. Thus the hydrocarbon gases have about one-tenth the solubility in water that they have in non-polar solvents at the same partial pressure. Benzene is miscible in all proportions with non-polar solvents.

2. The heats of solution of the hydrocarbon gases are negative and several fold greater in water than in the hydrocarbon solvents. Benzene has a minimum in the solubility curve at 16°C., thus indicating zero heat of solution. But of course if one dissolves benzene from the vapor phase one finds a very large negative heat of solution. There is no reason to assume any association in the hydrocarbons so that the solution must be assumed to be regular in the sense that entropy of solution ($-R \ln X$, where X is the mole fraction of the solute) must exist. For some cases this mole fraction is better calculated as a volume fraction. The low solubility requires a large negative entropy term to offset the positive entropy of dilution. This decrease in entropy must arise from some sort of interaction between solute and solvent.

The solubility of the hydrocarbon gases in water has been satisfactorily explained by Claussen[2-4] and his coworkers as due to the formation of the gas hydrates. These hydrates are clathrate type compounds which depend for this formation not on attractive forces between the hydrocarbon and water molecules, but rather on the lack of these attractive forces. Such van der Waals type of forces as exist are non-orienting and permit the water molecules to form hydrogen bonded structures which are more nearly perfect than those which exist in ice. This conclusion

is confirmed by the fact that these hydrates crystallize in the regular system. It can be shown by the customary criteria that these structures exist in solution as well as the solid phase, each gas molecule being surrounded by a cage of water molecules. This will account for negative enthalpy and entropy terms.

No hydrate is known in the case of benzene. Various reasons may be suggested for the non-existence of the hydrate. The benzene molecule is probably too large to fit into a stable structure. The possibility of orientation of water molecules at a benzene water interface cannot be denied but we shall see that we do not need to assume this to account for the solution entropy; rather if we do assume it we shall end by calculating too large a decrease in entropy. The thermodynamic properties of the solution can be accounted for without assuming structure. The heat of mixing which is exactly zero at 16°C. seems surprising at first in that the molal enthalpy of vaporization of benzene is considerably less than the molal enthalpy of vaporization of water. This point is offset, however, by the fact that the free surface energy per molecule of benzene is greater than the free surface energy per molecule of water. One needs only assume a better "fit" between benzene and water molecules to understand the zero heat of mixing. It can be supposed of course that part of this better fit is between the water molecules themselves since each benzene molecule is surrounded by several hundred water molecules. This would be accompanied by a decrease in entropy of magnitude comparable to the difference in the enthalpies of vaporization divided by the temperature.

It remains to account for the large negative entropy effect that occurs in the solution. Bohon and Claussen give the solubility of benzene as 0.023 moles per liter at 25°C. The heat of solution is 560 cal./mole. At equilibrium, $\Delta S = \Delta H/T = 1.9$ E. U.

The entropy of dilution calculated on a volume basis

$$\Delta S = R \ln \frac{1000}{0.023 \times 90} = 12.3 \text{ E. U.}$$

Hence $$1.9 = 12.3 + \Delta S^*$$

and $$\Delta S^* = -10.4 \text{ E. U.}$$

In the absence of other factors such as a large positive enthalpy of solution which usually accounts for the low solubility one is tempted to seek the explanation in terms of the internal pressure of water as compared to benzene. Certainly Hildebrand has adduced empirical evidence for the internal pressure as a measure of compatibility of liquids.

Internal pressure is of course not a pressure but a tension and the hypothetical pressure that is assumed depends upon the nature of the cavity in the liquid and the molecules within the cavity. No thermodynamic measurement can be made of it hence no thermodynamic significance can be attributed to it.

One is tempted to reason by analogy, however. The partial molal volume of benzene in water is less than that in benzene itself. This decrease of volume may be attributed to the compression of the benzene molecules by the environment of water molecules. This compression will decrease the partial molal entropy of benzene. One can write the quasi-thermodynamic equation

$$(\partial S/\partial V)_T = (\partial P/\partial T)_V = -(\partial P/\partial V)_T (\partial V/\partial T)_P$$

By substitution of $\alpha = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_P$, the coefficient of expansion and $\beta = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T$, the compressibility, one obtains

$$\Delta S^* = \int \frac{\alpha}{\beta} dV$$

The value of α has been measured for benzene in water solution and is found to be near that of benzene itself. The compressibility of benzene has not been measured accurately over a wide range of pressure and it is known to change rapidly with the pressure. The compressibility in pure benzene is not necessarily the value that is wanted here. There seems to be no possibility of measuring it in the water solution. Since the internal pressure of water is thought to be much higher than that of benzene a high degree of compression is assumed for the benzene molecule. Since we do not know the compressibility as a function of the pressure we shall assume an average value for β and replace the integral by the relation

$$\Delta S^* = \frac{\alpha}{\beta} \Delta V$$

Using the values $\alpha = 1.15 \times 10^{-3}$, $\beta = 25 \times 10^{-6}$, and $\Delta V = -6.4$ cm.,[3] we obtain on conversion to calories

$$\Delta S^* = 7.1 \text{ E. U.}$$

This assumption would account for the entropy of benzene in water. It will be noted that while the effect of the internal pressure is to decrease the solubility of benzene in water, an external pressure would have the opposite effect.

* Fellow of the Atomic Energy Commission. This paper is based on a portion of a thesis presented by Wm. L. Masterton in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of Illinois, June, 1953.

[1] Hildebrand, J. H., and Scott, R. L., *The Solubility of Nonelectrolytes*, Reinhold Publishing Corp., New York, 1950.

[2] Bohon, R. L., and Claussen, W. F., *J. Am. Chem. Soc.*, **75**, 1571 (1951).

[3] Claussen, W. F., *J. Chem. Phys.*, **19**, 259, 662, 1425 (1951).

[4] Claussen, W. F., and Polylase, M. F., *J. Am. Chem. Soc.*, **74**, 1751 (1951).

ON THE INTEGRATION OF KOLMOGOROFF'S DIFFERENTIAL EQUATIONS

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1. A Markoff chain corresponding to a system which can assume countably many states, with the property that the probability of a transition from state i at time t_1 to state j at time t_2 is a function of $i, j, t_2 - t_1$, determines a transition matrix $P(t) = (p_{ij}(t))$ such that

$$0 \leqq p_{ij}(t), \qquad \sum_{j=1}^{\infty} p_{ij}(t) \equiv 1, \qquad \lim_{t \to +0} p_{ij}(t) = \delta_{ij}, \tag{1}$$

$$p_{ij}(s+t) = \sum_{k=1}^{\infty} p_{ik}(s)p_{kj}(t), \qquad 0 < s, t < \infty. \tag{2}$$

If the probability of the system of being originally in state i be denoted by x_i, $\sum_i x_i = 1$, then the probability of its being in state j after the time t is given by

$$y_j = \sum_{i=1}^{\infty} p_{ij}(t)x_i, \qquad j = 1, 2, \ldots. \tag{3}$$

The matrix $P(t)$ also satisfies a pair of (systems of) differential equations one of which is

$$p'_{ij}(t) = \sum_{k=1}^{\infty} a_{ik}p_{kj}(t), \qquad i, j = 1, 2, \ldots, \tag{4}$$

where $A = (a_{ij})$ is a matrix of constants such that

$$a_{ij} \geqq 0, \quad i \neq j, \qquad a_{ii} \leqq 0, \qquad \sum_{j=1}^{\infty} a_{ij} = 0. \tag{5}$$

Replacing A by its transposed matrix, one obtains the other differential equations, both originally derived by A. Kolmogoroff.[1] The problem of integrating such systems, and even much more general ones, has been solved by W. Feller.[2]

2. In the present note a special case of the integration problem will be examined from the point of view of the theory of semi-groups of linear bounded operators.[3] Let $\mathfrak{M}$ be the Markoff algebra of matrices $B = (b_{ij})$ with complex elements such that

$$\|B\| = \sup_i \sum_{j=1}^{\infty} |b_{ij}| < \infty. \tag{6}$$

Every transition matrix is an element of $\mathfrak{M}$ of norm one and equation (2) expresses the semi-group property

$$P(s+t) = P(s)P(t). \tag{7}$$

$P(t)$ may be interpreted as an operator in several different ways. One of these attaches to equation (3); allowing the x_i's to be arbitrary complex numbers with $\sum_i |x_i| < \infty$, (3) defines a linear transformation of the space (l) into itself

$$\mathbf{y} = P(t)[\mathbf{x}], \qquad \mathbf{x} = (x_i), \qquad \mathbf{y} = (y_i) \tag{8}$$

of norm one and these transformations form a semi-group. A second interpretation is to let $P(t)$ act in $\mathfrak{M}$ as left multiplier so that

$$P(t)[B] = P(t)B = \left(\sum_{k=1}^{\infty} p_{ik}(t)b_{kj}\right) \tag{9}$$

is the matrix product. Again the norm is one and the transformations form a semi-group. The operator $P(t)$ is strongly continuous to the right at $t = 0$ provided the last condition under (1) holds uniformly for the diagonal elements. This is a very restrictive condition implying that $P(t) = \exp(tA)$, $A \in \mathfrak{M}$. In general we have strong continuity for $t \geqq 0$ only in a subspace $\mathfrak{M}_0$, non-dense in $\mathfrak{M}$.

The matrix A is normally not an element of $\mathfrak{M}$, but we may use A as an unbounded operator acting as a left multiplier in $\mathfrak{M}$, its domain $\mathfrak{D}[A]$ being the subset of $\mathfrak{M}$ for which the matrix product $AB \equiv A[B]$ is defined and is an element of $\mathfrak{M}$. We set $\overline{\mathfrak{D}[A]} = \mathfrak{M}_A$.

For $B \in \mathfrak{D}[A^2]$ the Cauchy problem

$$\begin{aligned} &Y'(t) = A[Y(t)], \qquad Y(t) \in \mathfrak{D}[A], \qquad t > 0, \\ &\lim_{t \to +0} \|Y(t) - B\| = 0, \end{aligned} \tag{10}$$

has the unique solution $Y(t) = P(t)[B]$. This suggests that some contraction of A is the infinitesimal generator in $\mathfrak{M}_A$ of the semi-group $\{P(t)\}$. Conversely, given a matrix A satisfying conditions (5), we may interpret it as an operator in $\mathfrak{M}$ and we may ask if it generates a semi-group in $\mathfrak{M}_A$ and, in particular, if the semi-group is defined by a transition matrix satisfying (1) and (2).

3. We shall solve this problem for triangular matrices

$$A = (a_{ij}), \qquad a_{ij} = 0, \qquad j > i, \tag{11}$$

satisfying conditions (5). Here it is easy to prove that a contraction of A generates a semi-group of transition operators in $\mathfrak{M}_A$ and the general theory of semi-groups gives a method of calculating $P(t)$.

The product AB always exists in this case and $\mathfrak{D}[A]$ is the set of matrices B in $\mathfrak{M}$ such that

$$\sup_i \sum_{j=1}^{\infty} \left| \sum_{k=1}^{i} a_{ik}b_{kj} \right| < \infty. \tag{12}$$

If A is not in $\mathfrak{M}$, the sphere $\|X - I\| < 1/2$ is not in $\mathfrak{D}[A]$ and, consequently, $\mathfrak{D}[A]$ is not dense in $\mathfrak{M}$.

It is easily seen that if λ is not equal to any of the diagonal elements a_{ii}, then the characteristic equation

$$(\lambda I - A)X = 0 \tag{13}$$

has no solutions in $\mathfrak{M}$ except the zero matrix, while if $\lambda = a_{ii}$ there are other solutions. Thus the point spectrum of A as left multiplier in $\mathfrak{M}$ coincides with the set $\{a_{ii}\}$. Consider next the equation

$$(\lambda I - A)Y = I \tag{14}$$

for $\lambda \neq a_{ii}$. There is a unique solution $Y = R(\lambda) = \{r_{jk}(\lambda)\}$ and the system of equations

$$\sum_{k=1}^{i} (\lambda\delta_{ik} - a_{ik})r_{kj}(\lambda) = \delta_{ij}, \qquad i, j = 1, 2, 3, \ldots \tag{15}$$

gives the following properties for the $r_{jk}(\lambda)$:

(i) $r_{jk}(\lambda) \equiv 0$ for $k > j$;

(ii) $r_{jj}(\lambda) = (\lambda - a_{jj})^{-1}$;

(iii) each $r_{jk}(\lambda)$ with $k < j$ is a rational function of λ, zero at infinity and having poles at $\lambda = a_{mm}$, $k \leqq m \leqq j$, the poles being simple if the a_{mm} are distinct;

(iv) $r_{jk}(\lambda) > 0$ for $k \leqq j$, $\quad \lambda > 0$;

(v) $R_i(\lambda) \equiv \sum_{k=1}^{i} r_{ik}(\lambda) \equiv \lambda^{-1}$ for each i.

These properties are proved by induction using (15); (iv) is obviously true for $k = j$ and (v) holds for $i = 1$ since $a_{11} = 0$. To verify (v) one adds equations (15) for $j = 1, 2, \ldots, i$, obtaining the identity

$$\sum_{k=1}^{i} (\lambda\delta_{ik} - a_{ik})R_k(\lambda) \equiv 1, \tag{16}$$

holding for every i. These equations determine the $R_k(\lambda)$ uniquely and are obviously satisfied by $R_k(\lambda) = \lambda^{-1}$ for every k.

$R(\lambda)$ is evidently also a triangular matrix and it belongs to $\mathfrak{D}[A]$ at least for $\lambda > 0$ by virtue of (iv) and (v). Conversely, if $\lambda > 0$ and if $B \in \mathfrak{D}[A]$, then there exists a matrix $C \in \mathfrak{M}$ such that $B = R(\lambda)[C]$. In fact, $C = \lambda B - AB$. By definition the domain of A is dense in $\mathfrak{M}_A$. That A is closed in $\mathfrak{M}_A$ is proved by the usual argument: if $\{B_n\}$ and $\{C_n\} = \{AB_n\}$ are two Cauchy sequences in $\mathfrak{D}[A]$ and $\mathfrak{M}_A$ converging to B_0 and C_0, respectively, then $B_n = R(\lambda)(\lambda B_n - C_n)$ gives in the limit $B_0 = R(\lambda)(\lambda B_0 - C_0)$ so that $B_0 \in \mathfrak{D}[A]$ and $AB_0 = C_0$.

It follows that

$$R(\lambda) \equiv R(\lambda; A) \tag{17}$$

is the resolvent of A at least for $\lambda > 0$.

Let us now consider $\lambda R(\lambda; A)$ for $\lambda > 0$ as an operator in $\mathfrak{M}$. The norm of the transform equals

$$\begin{aligned} \|\lambda R(\lambda; A)[B]\| &= \sup_i \lambda \sum_{j=1}^{\infty} \left| \sum_{k=1}^{i} r_{ik}(\lambda) b_{kj} \right| \\ &\leqq \sup_i \lambda \sum_{k=1}^{i} r_{ik}(\lambda) \sum_{j=1}^{\infty} |b_{kj}| \end{aligned} \tag{18}$$

and (v) shows that this expression is at most equal to $\|B\|$ with equality if every $b_{kj} \geqq 0$ and $\sum_j b_{kj} = \|B\|$ for each k, that is, when B is a positive multiple of a transition matrix. Thus $\lambda R(\lambda; A)$ is a transition operator in $\mathfrak{M}$. Except for the fact that $\mathfrak{D}[A]$ is not dense in $\mathfrak{M}$, the assumptions of the Hille-Yosida theorem[4] are satisfied; the proof applies and gives the existence of a semi-group of transition operators $\{P(t)\}$, strongly continuous for $t \geqq 0$ when acting in $\mathfrak{M}_A$. According to Yosida

$$P(t)[B] = \operatorname*{str\,lim}_{n \to \infty} \exp\,(tn\,AR(n;\,A))[B], \tag{19}$$

valid in $\mathfrak{M}_A$. If $B \in \mathfrak{M}_A$, then the expression after the limit is also in $\mathfrak{M}_A$, hence so is $P(t)[B]$. Denoting the infinitesimal generator of $P(t)$ by A_0, one sees that the assumption $B \in \mathfrak{D}[A_0]$ implies $A_0[B] \in \mathfrak{M}_A$.

Formula (19) implies that

$$\int_0^\infty e^{-\lambda t} P(t)[B]\,dt = \operatorname*{str\,lim}_{n \to \infty} \int_0^\infty e^{-\lambda t} \exp\,(tn\,AR(n;\,A))[B]\,dt.$$

Here the integral on the right equals

$$(\lambda I - nAR(n;\,A))^{-1}[B] = \left\{\frac{I}{\lambda + n} + \left(\frac{n}{\lambda + n}\right)^2 R\left(\frac{n\lambda}{\lambda + n};\,A\right)\right\}[B] \tag{20}$$

and this has the limit $R(\lambda;\,A)[B]$ as $n \to \infty$ while the integral on the left equals $R(\lambda;\,A_0)[B]$ so that

$$R(\lambda;\,A)[B] = R(\lambda;\,A_0)[B], \qquad B \in \mathfrak{M}_A. \tag{21}$$

Hence if $B \in \mathfrak{D}[A_0]$ one has $B = R(\lambda;\,A_0)(\lambda I - A_0)B$ and by (21) this equals $R(\lambda;\,A)(\lambda I - A_0)B$ so that $B \in \mathfrak{D}[A]$ and $A_0[B] = A[B]$. On the other hand, if $B \in \mathfrak{D}[A]$ and $A[B] \in \mathfrak{M}_A$, one sees that $B \in \mathfrak{D}[A_0]$ and $A[B] = A_0[B]$. Thus A_0 is the contraction of A to the subset of $\mathfrak{D}[A]$ in which $A[B] \in \mathfrak{M}_A$. We note that $\mathfrak{D}[A^2] \subseteq \mathfrak{D}[A_0] \subseteq \mathfrak{D}[A]$.

The stated properties of A and $P(t)$ show that the matrix elements $p_{ij}(t)$ satisfy conditions (1), (2), and (5). Since $R(n;\,A)$ and $AR(n;\,A)$ are triangular matrices, one concludes from (19) that so is $P(t)$. For the actual computation of $P(t)$ one had better use the complex inversion formula.[5] The latter gives $P(t)[B]$ as the inverse Laplace transform of $R(\lambda;\,A)[B]$; the arbitrariness of B (in $\mathfrak{D}[A_0]$) implies corresponding relations for the matrix elements, that is,

$$p_{jk}(t) = \lim_{\omega \to \infty} \frac{1}{2\pi i} \int_{\alpha - i\omega}^{\alpha + i\omega} e^{\lambda t} r_{jk}(\lambda)\,d\lambda, \tag{22}$$

where $\alpha > 0$. Hence each $p_{jk}(t)$ with $k \leqq i$ is an exponential polynomial, having the form

$$p_{jk}(t) = \sum_{m=k}^{j} c_{jk}^m \exp\,(a_{mm}t), \tag{23}$$

if the exponents are distinct, otherwise powers of t also occur.

6. If $B \in \mathfrak{D}[A_0]$, one knows that

$$\frac{d}{dt} P(t)[B] = AP(t)B = P(t)AB. \tag{24}$$

Since this holds for every matrix B in $\mathfrak{D}[A_0]$, one must have

$$P'(t) = AP(t) = P(t)A, \tag{25}$$

so that $P(t)$ satisfies both equations of Kolmogoroff. While $P(t)[B]$ is the only solution of (10), $z_{ij}(t) = p_{ij}(t)$ is not necessarily the only solution of

$$Z'(t) = Z(t)A, \qquad Z(t) = \{z_{ij}(t)\}, \qquad \lim_{t \to +0} z_{ij}(t) = \delta_{ij}. \tag{26}$$

In fact the properties of A as a multiplier in $\mathfrak{M}$ may be entirely different for right and left multiplication. An adaptation of an example due to W. Feller[6] will illustrate this. Take $a_{ij} = 0$ unless $j = i - 1$ or i and let

$$a_{i,\ } = -a_{i,\ i} = \beta_i, \qquad \sum_2^\infty \beta_i^{-1} < \infty. \tag{27}$$

This is a triangular matrix so the point spectrum of A for left multiplication is the set $\{-\beta_i\}$. But the characteristic equation for right-hand multiplication

$$X[\lambda I - A] = 0$$

has solutions in $\mathfrak{M}$ for every λ and we can choose $X = X(\lambda)$ so that $X(\lambda)$ is bounded and holomorphic for $\Re(\lambda) \geqq \epsilon > 0$ and $\|\lambda X(\lambda)\| \epsilon L(-\infty, \infty)$ on every vertical line $\Re(\lambda) = \alpha > 0$. Such a choice is given by $X(\lambda) = \{x_{mn}(\lambda)\}$ where

$$x_{m1}(\lambda) = \lambda^{-1}(1 + \lambda)^{-3} \prod_2^\infty \left(1 + \frac{\lambda}{\beta_k}\right)^{-1}, \qquad x_{mn}(\lambda) = \frac{1}{\beta_n}(1 + \lambda)^{-3} \prod_n^\infty \left(1 + \frac{\lambda}{\beta_k}\right)^{-1}, \quad n > 1.$$

With the aid of such an $X(\lambda)$ we construct the nul solution[7]

$$Z(t) = \frac{1}{2\pi i} \int_{\alpha - i\infty}^{\alpha + i\infty} e^{\lambda t} X(\lambda)\, d\lambda. \tag{28}$$

This is a solution in $\mathfrak{M}$ of the differential equation in (26) but it tends strongly to zero as $t \to 0$. It follows that the solution of (26) cannot be unique in $\mathfrak{M}$ for this special choice of A.

Similar phenomena arise when a triangular matrix A is interpreted as an operator in (l) defined by replacing $p_{ij}(t)$ in (3) by a_{ij}. Thus in the special case (27) the point spectrum of A in (l) also covers the whole plane and associated differential equations have nul solutions.

[1] Kolmogoroff, A., "Über die analytischen Methoden in der Wahrscheinlichkeitsrechnung," *Math. Ann.*, **104**, 415–458 (1931). For a derivation under more general assumptions, see pp. 386–391 of Feller, W., *An Introduction to Probability Theory and Its Applications*, John Wiley & Sons, Inc., New York, 1950.

[2] Feller, W., "On the Integrodifferential Equations of Purely Discontinuous Markoff Processes," *Trans. Am. Math. Soc.*, **48**, 488–515 (1940).

[3] See Hille, E., "Functional Analysis and Semi-Groups," *Am. Math. Soc. Colloquium Publications*, Vol. 31, New York, 1948. The Markoff algebra is discussed in § 21.3; differential equations of the Kolmogoroff type and properties of $P(t)$ as an operator in (l) are derived there, but not the interpretation of $P(t)$ as an operator in $\mathfrak{M}$. See also the early papers of K. Yosida on semi-group theory, especially "On the Differentiability and the Representation of One-Parameter Semi-Group of Linear Operators," *J. Math. Soc. Japan*, **1**, 15–21 (1948), and "An Operator-Theoretical Treatment of Temporally Homogeneous Markoff Process," *Ibid.*, **1**, 244–253 (1949). In a letter of October 24, 1953, Dr. Tosio Kato, Department of Physics, University of Tokyo, informed me that he had carried through the integration problem for Kolmogoroff's equations by semi-group theory working in the space (l).

[4] See the references in the preceding footnote. Hille, *loc. cit.*, Chapter XII, treats essentially

only contraction operators and this is also the case considered by Yosida in his first paper. The extension to transition operators occurs in his second paper.

[5] Hille, *loc. cit.*, p. 232, formula (11.7.2).

[6] See the references in footnotes 1 and 2. In the former, consult pages 391–394.

[7] The construction here indicated is an application of a general method used by the author in, for instance, "Sur le problème abstrait de Cauchy," *Compt. rend. Acad. Sci., Paris*, **236**, 1466–1467 (1953). Since all the functions $x_{mn}(\lambda)$ are completely monotone for $\lambda > 0$, the functions $z_{mn}(t)$ will be non-negative, and $Z(t)$ is a positive nul solution. The existence of positive nul solutions for related systems has been proved by W. Feller, *loc. cit.*, using other methods.

AN APPLICATION OF HIGH-SPEED COMPUTING TO FERMAT'S LAST THEOREM

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Introduction.—The statement of Fermat (known as Fermat's Last Theorem), which dates from 1672, that

$$x^n + y^n = z^n, \qquad n > 2, \tag{1}$$

has no non-zero solutions in integers still awaits a proof or disproof. It is known that for a proof it is sufficient to consider the case of $n = l$, an odd prime.

With the assumption that xyz is not divisible by l (known as case (1)), very stringent criteria on (1) have been devised and it was shown by D. H. and Emma Lehmer[1] in 1941 that (1) is impossible for each $l \leqq 253{,}747{,}899$ in this case.

Without the restriction to case (1) the problem appears to be much more difficult and requires the consideration of each prime l individually. In this connection Kummer defined a prime l to be *regular* in case it does not divide any of the first $(l-3)/2$ Bernoulli numbers

$$B_1 = {}^1/_6, \qquad B_2 = {}^1/_{30}, \ \ldots$$

and gave a proof in 1850 that (1) is impossible for regular primes (Theorem I). Kummer in 1857, and 1874 also, found the eight *irregular* primes less than 164 and devised criteria which he applied to all such primes excepting 101, 103, 131, and 149. This, using his result on regular primes also, enabled him to prove Fermat's Last Theorem for all primes $l < 164$ with the exceptions just mentioned, and the additional exception $l = 157$ when his criteria failed.

During the years 1928–1936 a number of collaborators at the University of Texas under the direction of H. S. Vandiver examined the primes <619 and developed criteria (Theorem II) which proved Fermat's Last Theorem for the 36 primes which were found to be irregular <619 including $l = 157$. At this point the calculations became prohibitively long and laborious for desk calculator work.

It is the object of this paper to show how this program has been carried out for all primes less than 2000 in a few hours using the high-speed calculating machine of the National Bureau of Standards known as the SWAC at the Institute for Numerical Analysis in Los Angeles, as coded by D. H. and Emma Lehmer. As before,

the calculations were in two parts: the determination of irregular primes, and the application of criteria to prove Fermat's Last Theorem for these primes. The first revealed the interesting fact that nearly half the primes <2000 are irregular. For the second part it was necessary to modify the criterion used by Vandiver to make it applicable for high-speed calculation. Some details of this will be discussed in what follows together with the presentation of the results in tabular form. *Besides proving Fermat's Last Theorem for all $l < 2000$, these results have applications to the theory of cyclotomic fields* which will be discussed by Vandiver in another paper.

Determination of the Regular and Irregular Primes < 2000.—The first of Kummer's results (1850) already referred to is specifically as follows:[2]

THEOREM I. *If l is a given regular prime, then*

$$x^l + y^l + z^l = 0 \tag{2}$$

is impossible for rational integers x, y, and z, none zero.

Kummer's[3] second criterion (1857) is not employed in this paper. However, all the criteria for (1) which have been obtained since and which are not subject to the restriction of case (I) have stemmed from it.

Consider the cyclotomic algebraic field, designated by K, or $K(\zeta)$, where ζ is a primitive lth root of unity with l as before an odd prime. Let $k_i = \zeta^{r^i/2} - \zeta^{-r^i/2}$ and $e_i = k_{i+1}/k_i$ with r a primitive root of l. Set

$$E_n(\zeta) = E_n = \prod_{i=0}^{(l-3)/2} e_i^{r^{-2\,in}}. \tag{3}$$

With these definitions we may state the second criterion which we shall use as follows:

THEOREM II. *Under the following assumption: none of the units E_a (defined in (3)) with $a = a_1, a_2, \ldots, a_s$ (see (4)) is congruent to an lth power of an integer in $K(\zeta)$ modulo $\mathfrak{p}$, where $\mathfrak{p}$ is a prime ideal divisor of (p), with p a rational prime $< l^2 - l$ of the form $1 + kl$; (2) is impossible in non-zero rational integers.*

In testing the criteria of Theorems I and II, it is first necessary to determine if l is regular, and if it is not, to determine all the s distinct $a_1, a_2, \ldots, a_s$ in the set 1, 2, 3, $\ldots$, $(l-3)/2$ such that

$$B_{a_1}, B_{a_2}, \ldots, B_{a_s} \tag{4}$$

are each divisible by l.

In order to obtain this information we must examine the first $(l-3)/2$ Bernoulli numbers B_n (modulo l). This is best done by using one of the many congruences expressing Bernoulli numbers modulo l as sums of like powers. Such a formula, which involves the least number of terms, is the following[5]

$$S_a = \sum_{l/6 < s < l/4} s^{2a-1} \equiv (-1)^a(2^{l-2a} - 1)(3^{l-2a} - 2^{l-2a} - 1)B_a/4a, \qquad (l > 7,\ 2a < l-1). \tag{5}$$

The only drawback of this formula is that for some a's the factor

$$f_a = (2^{l-2a} - 1)(3^{l-2a} - 2^{l-2a} - 1)$$

is itself divisible by l, thus leaving the divisibility of B_a in doubt in these cases.

However, if $S_a \not\equiv 0 \pmod{l}$ for all a, then l is regular. The SWAC was programmed to calculate S_a (modulo l) for all $a = 1, 2, \ldots, (l-3)/2$ in succession and to punch out on cards the values of l and a for which $S_a \equiv 0 \pmod{l}$. The SWAC was also instructed to accumulate the sum

$$S = \sum_{a=1}^{\mu} S_a \pmod{l}, \qquad \mu = (l-1)/2,$$

and to test whether $S \equiv 0 \pmod{l}$, as it should be, before proceeding to the next prime l. If S failed to be congruent to zero, the SWAC was instructed to stop; such a contingency did not arise, however, and the operation was completely automatic. The output of this run, consisting of cards with values of l and a punched on them, was then fed back into the machine and the machine was asked to examine the factor f_a (modulo l). If this factor was not divisible by l, then the SWAC was instructed to punch out another card with the values of l and a together with a code word indicating that the prime l was *irregular with index a*. If $f_a \equiv 0 \pmod{l}$, however, the machine was instructed to try another congruence,[5] namely

$$S_a' = \sum_{l/6 < s < l/5} s^{2a-1} + \sum_{l/3 < s < 2l/5} s^{2a-1} \equiv (-1)^a f_a' B_a/4a, \qquad (l > 5,\ 2a < l-1) \quad (6)$$

containing $[l/10]$ terms; provided the factor

$$f_a' = 6^{l-2a} - 5^{l-2a} - 2^{l-2a} + 1$$

was not divisible by l. Then if S_a' turned out not to be divisible by l, neither was B_a and this particular output of run (I) was merely a false alarm due to the divisibility of f_a by l and was to be disregarded. On the other hand, if $S_a' \equiv 0 \pmod{l}$, then l is irregular with index a and this was recorded on an output card as before. However, if the factor f_a' was divisible by l as well as f_a, then uncertainty prevailed and it was necessary to resort to a much longer formula of $[l/2]$ terms which, however, gives unequivocal results in all cases, namely[5]

$$S_a'' = \sum_{r=1}^{\mu} (l-2r)^{2a} \equiv (-1)^{a-1} 2^{2a-1} l B_a \pmod{l^3}. \qquad (7)$$

Although this formula holds modulo l^3, it was sufficient to carry out the calculations modulo l^2. In each case it was tested as a check that $S_a'' \equiv 0 \pmod{l}$ and a card was punched every time $S_a'' \equiv 0 \pmod{l^2}$.

The output of run (II) was then a set of cards giving all the irregular primes with their indices of irregularity a_i. These will be found in the first two columns of our table. We shall call the number of indices of irregularity for a given l the *degree of irregularity* of l. The largest degree so far found is three.

For $l < 619$, these results were checked against those found by Vandiver and his collaborators.[6] They were found to agree except that $l = 389$ and $l = 613$ were found to be irregular instead of regular, and the value of $2a = 338$ (or $a = 119$) for $l = 491$, given in the table of the present paper, had not been previously found. Further tests showed the SWAC figures to be correct.

As to the frequency of irregular primes, there are 184 regular and 118 irregular primes less than 2000. The following distribution table may be of interest. We

divide the interval up to 2000 into eight equal parts and let $250k < l < 250(k+1)$, $k = 0, 1, \ldots, 7$.

	$k=0$	1	2	3	4	5	6	7	TOTAL
No. of irregular primes	9	19	20	16	11	14	11	18	118
No. of primes	52	42	37	36	36	35	33	31	302
Percentages, irregular primes	17	45	54	44	31	40	33	58	39

Jensen[7] proved that there exist an infinity of irregular primes of the form $4n + 3$. There is nothing in the table to indicate that there is only a finite number of regular primes. It is well to note this situation, as a number of theorems in the theory of regular cyclotomic fields have been given which do not appear to extend to irregular fields.

If we consider only divisors of the numerators of Bernoulli numbers (in their lowest terms) which are prime to their indices, then a regular prime divides the numerator of no Bernoulli number. An irregular prime divides the numerators of an infinity of Bernoulli numbers.

Treatment of the Irregular Primes.—For this purpose we employ the criterion given in Theorem II. To use this on the SWAC it was necessary to replace the quantity E_a by another simpler quantity in K. For this we need the

LEMMA. *Let t be any integer such that $t^k \not\equiv 1 \pmod{p}$ where p is a prime of the form $p = kl + 1 < l^2 - l$. Define Q_a by*

$$Q_a = t^{-kd/2} \prod_{b=1}^{\mu} (t^{kb}-1)^{b^{l-1-2a}}, \tag{8}$$

where $\mu = (l-1)/2$ and

$$d = 1^{l-2a} + 2^{l-2a} + \ldots + \mu^{l-2a}.$$

Then the unit E_a is congruent to the lth power of an integer in $K(\zeta)$ modulo a prime ideal dividing (p), if, and only if,

$$Q_a^k \equiv 1 \pmod{p}. \tag{9}$$

For proof let

$$R(q) = \zeta^q - \zeta^{-q}; \qquad A = \prod_{i=1}^{\mu} R(r^i)^{r^{-2a(i-1)}}; \qquad B = \prod_{j=0}^{\mu-1} R(r^j)^{r^{-2aj}}. \tag{10}$$

Then

$$E_a(\zeta^2) = A/B. \tag{11}$$

We first note that

$$B^{r^{2a}-1} = E_a(\zeta^2)\rho_1^l. \tag{12}$$

For, we have

$$A^{r^{-2a}} = B\rho_2^l.$$

This follows if we note that $R(r^\mu) = -R(r^0)$ since r is a primitive root of l and $r^\mu \equiv -1 \pmod{l}$, with $(-1) = (-1)^l$. From this we obtain $B^{r^{2a}-1} = (A/B)\rho_2^l$ and with (11) we get (12), where ρ_1 and ρ_2 are numbers in K, whose denominator, if any, can

be put in the form $(\zeta - 1)^h$, with h a positive rational integer. The same statement will hold for $\rho_3, \rho_4, \ldots, \rho_{18}$ in what follows.

Now also, in a similar way,

$$R(r^k) = -R(r^{k+\mu})$$

if $k = 0, 1, \ldots, \mu - 1$ and

$$R(r^k)^{r-2ak} = R(r^{k+\mu})^{r-2ak}\,\rho_3^l.$$

Now

$$r^{-2ak} \equiv r^{-2a(\mu+k)} \pmod{l},$$

since $r^{2\mu} \equiv 1 \pmod{l}$, and hence

$$R(r^k)^{r-2ak} = R(r^{k+\mu})^{r-2a(k+\mu)}\,\rho_4^l.$$

Whence,

$$B^2 = \prod_{h=0}^{l-2} R(r^h)^{r-2ah}\,\rho_5^l,$$

and since, modulo l; $1, r, r^2, \ldots, r^{l-2}$ are congruent to the integers $1, 2, \ldots, l-1$ in some order

$$B^2 = \prod_{n=1}^{l-1} R(n)^{n-2a}\,\rho_6^l. \tag{13}$$

We have

$$R(b) = -R(l-b), \qquad R(b)^{b-2a} = R(l-b)^{(l-b)-2a}\,\rho_7^l;$$

whence, when we replace $(-2a)$ by $(l-1-2a)$ which only changes ρ_7,

$$\prod_{b=1}^{\mu} R(b)^{bl-1-2a} = \prod_{b=1}^{\mu} R(l-b)^{(l-b)l-1-2a}\,\rho_8^l.$$

Then, since

$$(l-b)^{l-1-2a} \equiv b^{l-1-2a} \pmod{l},$$

(13) gives

$$B^2 = \prod_{b=1}^{\mu} R(b)^{2bl-1-2a}\,\rho_9^l.$$

Select c so that $2c \equiv 1 \pmod{l}$, then $B^{2c} = B\rho_{10}^l$, and similarly on the right so that

$$B = \prod_{b=1}^{\mu} R(b)^{bl-1-2a}\,\rho_{11}^l. \tag{14}$$

Now using (12) and raising it to the mth power with $m(r^{2a}-1) \equiv 1 \pmod{l}$, noting that $(l, r^{2a}-1) = 1$, we have from (14)

$$\prod_{b=1}^{\mu} R(b)^{bl-1-2a} = E_a(\zeta^2)^m\,\rho_{12}^l, \tag{15}$$

or

$$\zeta^{-d} \prod_{b=1}^{\mu} (\zeta^{2b}-1)^{bl-1-2a} = E_a(\zeta^2)^m \rho_{12}^l. \tag{16}$$

Setting $\zeta^{(l+1)/2}$ for ζ in (16) then gives

$$\zeta^{-d/2} \prod_{b=1}^{\mu} (\zeta^{b}-1)^{bl-1-2a} = E_a(\zeta)^m \rho_{13}^l. \tag{17}$$

We easily see, using the methods similar to those employed in obtaining (12) and (13), that

$$E_a(\zeta^r) = (E_a(\zeta))^{r^{2a}} \rho_{14}^l, \tag{18}$$

where r as before is a primitive root of l. Set $r^v \equiv n \pmod{l}$ for any n such that $(n, l) = 1$. Then repeated application of (18) gives

$$E_a(\zeta^{r^v}) = E_a(\zeta)^{r^{2av}} \rho_{15}^l$$

and

$$E_a(\zeta^n) = E_a(\zeta)^{n^{2a}} \rho_{16}^l. \tag{19}$$

Then (17) gives

$$\zeta^{-nd/2} \prod_{b=1}^{\mu} (\zeta^{bn}-1)^{bl-1-2a} = E_a(\zeta)^{n^{2a}m} \rho_{17}^l. \tag{20}$$

If g is a primitive root of p, then consider the ideal

$$(g^k - \zeta, p) = \mathfrak{p} \tag{21}$$

which divides (p), where $p = 1 + kl$. Let t be a rational integer such that $t^k \not\equiv 1 \pmod{p}$. Set $t \equiv g^n \pmod{p}$, then $n \not\equiv 0 \pmod{l}$; otherwise, $t^k \equiv 1 \pmod{p}$ when we note that $t^{p-1} \equiv 1 \pmod{p}$. Then $t^k \equiv g^{nk} \pmod{p}$; and using (21) $g^k \equiv \zeta \pmod{\mathfrak{p}}$ gives

$$t^k \equiv \zeta^n \pmod{\mathfrak{p}}. \tag{22}$$

Now from (20) we obtain, using (22),

$$t^{-kd/2} \prod_{b=1}^{\mu} (t^{kb}-1)^{bl-1-2a} \equiv E_a(\zeta)^{n^{2a}m} \rho_{18}^l \pmod{\mathfrak{p}} \tag{23}$$

noting that the denominator of ρ_{17}, if any, may be put in the form $(1 - \zeta)^h$, prime to $\mathfrak{p}$. Hence, setting Q_a for the left-hand member, we find

$$Q_a^k \equiv E_a(\zeta)^{n^{2a}mk} \pmod{\mathfrak{p}}.$$

Noting that $(n^{2a}m, l) = 1$, we see that $E_a(\zeta)$ is congruent to an lth power in K, modulo $\mathfrak{p}$ if, and only if,

$$Q_a^k \equiv 1 \pmod{p}.$$

This proves the lemma.[8]

Then we may state the

THEOREM III. *Let Q_a be defined as in the lemma and let*

$$B_{a_1}, B_{a_2}, \ldots, B_{a_s} \tag{24}$$

be the only Bernoulli numbers, with indices less than $(l-1)/2$, *which are divisible by* l. *Then if*

$$Q_{a_i}^k \not\equiv 1 \pmod{p}$$

holds for $i = 1, 2, \ldots, s$, *Fermat's Last Theorem holds for the exponent* l.

The above criterion was coded on the SWAC, which was instructed to calculate for each card giving an irregular prime l and its index a, first of all, the least prime p of the form $kl + 1$; it was then programmed to find out whether $2^k \equiv 1 \pmod{p}$ and was prepared to ask the same question about $3^k, \ldots$, etc. if this were the case. However, in all cases tested $2^k \not\equiv 1 \pmod{p}$, so that 2 was used for t in the expression for Q in all cases. After these preliminary calculations, the SWAC proceeded to calculate d. This was done modulo l, then $2^{-kd/2}$ was calculated modulo p and was multiplied by the successive factors in the product; after each multiplication a reduction modulo p was performed by the SWAC. Finally the value of Q_a (modulo p) thus obtained was raised to the kth power (mod p) and compared with unity. Considering the complicated form of the expression for Q_a above, it was rather gratifying to be able to code this whole calculation into the high-speed memory of the SWAC and to be able to perform the test in less than three minutes for our largest prime tested. In all cases the test held for the smallest p tried and the values of p were much smaller than permitted in the Theorem. However, if for some l, p should exceed $l^2 - l$ one can have recourse to a Theorem recently proved by Inkeri[9] to the effect that p can be $< {}^3/_2\,(l^2-l)$ in the statement of Theorems II and III.

Below is a table giving the values of l, $2a$, p, Q_a *and* Q_a^k *for all irregular* l*'s* < 2000. l *is the odd prime exponent in the Fermat relation,* $p = 1 + kl$, Q_a *is the left-hand member of* (23), *and* $2a$ *is twice the index of the Bernoulli numbers defined in* (24) (*that is, for example, if* $l = 647$, *the table gives us the information that the set* (24) *for this value of* l *consists of* B_{113}, B_{121}, *and* B_{277}). *If a prime* <2000 *does not appear in the column for* l, *this indicates that* l *is a regular prime.*

l	$2a$	p	Q_a	Q_a^k	l	$2a$	p	Q_a	Q_a^k
37	32	149	146	81	353	186	4943	1508	3144
59	44	709	137	645	353	300	4943	1088	3660
67	58	269	73	180	379	100	4549	111	4062
101	68	607	514	47	379	174	4549	784	1992
103	24	619	273	389	389	200	9337	1937	8328
131	22	263	91	128	401	382	3209	656	719
149	130	1193	420	178	409	126	1637	609	1506
157	62	1571	1293	102	421	240	4211	3155	2825
157	110	1571	170	1261	433	366	1733	772	496
233	84	467	276	55	461	196	2767	1756	1023
257	164	1543	1371	1258	463	130	5557	1850	5212
263	100	1579	1154	1385	467	94	2803	1742	1536
271	84	1627	951	367	467	194	2803	2051	655
283	20	1699	1388	383	491	292	983	289	949
293	156	587	88	113	491	336	983	213	151
307	88	1229	266	151	491	338	983	17	289
311	292	1867	523	360	523	400	5231	3924	3532
347	280	2083	1561	1711	541	86	9739	5189	7221

l	$2a$	p	Q_a	Q_a^k
547	270	5471	1797	3692
547	486	5471	4814	1597
557	222	3343	49	204
577	52	2309	447	1285
587	90	8219	4046	7886
587	92	8219	1960	126
593	22	1187	916	1034
607	592	3643	2811	815
613	522	6131	3872	513
617	20	4937	498	3740
617	174	4937	2952	832
617	338	4937	3569	3592
619	428	2477	1553	794
631	80	6311	1275	2592
631	226	6311	2939	1278
647	236	9059	8095	8931
647	242	9059	3009	7667
647	554	9059	5918	6916
653	48	1307	838	385
659	224	1319	42	445
673	408	2693	2442	2170
673	502	2693	1740	1879
677	628	5417	811	372
683	32	1367	1332	1225
691	12	6911	5642	73
691	200	6911	3360	4497
727	378	2909	1627	812
751	290	4507	3689	1519
757	514	12113	5256	6303
761	260	1523	455	1420
773	732	4639	1332	3942
797	220	4783	1389	2097
809	330	1619	582	353
809	628	1619	1502	737
811	544	8111	3823	6231
821	744	6569	2809	1240
827	102	11579	3683	5688
839	66	10069	4287	4868
877	868	14033	9707	11792
881	162	15859	10672	9493
887	418	5323	3952	4987
929	520	7433	2849	6592
929	820	7433	5250	7415
953	156	1907	1736	636
971	166	5827	1579	1835
1061	474	6367	1932	4808
1091	888	6547	3844	2117
1117	794	6703	2639	60
1129	348	4517	2385	4122
1151	534	6907	4263	3614
1151	784	6907	5747	5121
1151	968	6907	1825	5286
1153	802	25367	18794	18498
1193	262	7159	4936	325
1201	676	7207	5578	114
1217	784	29209	16956	1782
1217	866	29209	3569	21587
1217	1118	29209	6021	13160
1229	784	2459	1408	510
1237	874	19793	5866	18934
1279	518	12791	2027	5662
1283	510	7699	259	6117
1291	206	12911	9593	7683
1291	824	12911	443	85
1297	202	5189	2520	4344
1297	220	5189	1535	4324
1301	176	26021	21535	18702
1307	382	10457	5164	4993
1307	852	10457	1770	9922
1319	304	23743	9120	3063
1327	466	5309	585	3740
1367	234	10937	9041	9634
1409	358	2819	2022	934
1429	996	5717	4436	4539
1439	574	2879	2529	1582
1483	224	14831	14248	2174
1499	94	2999	2747	525
1523	1310	21323	6867	10522
1559	862	3119	337	1285
1609	1356	16091	12146	1078
1613	172	9679	8955	4873
1619	560	12953	3483	9010
1621	980	29179	15527	12268
1637	718	62207	3233	53518
1663	270	6653	520	2691
1669	388	16691	12078	1513
1669	1086	16691	8744	8989
1721	30	34421	12804	14618
1733	810	3467	1656	3406
1733	942	3467	2234	1743
1753	712	7013	1117	4910
1759	1520	31663	13295	29437
1777	1192	7109	5718	6072
1787	1606	10723	3556	7206
1789	848	17891	9604	11296
1789	1442	17891	12106	14937
1811	550	3623	3618	25
1811	698	3623	539	681
1811	1520	3623	2898	290
1831	1274	10987	1860	2735
1847	954	11083	3187	3360
1847	1016	11083	5462	1029

l	$2a$	p	Q_a	Q_a^*	l	$2a$	p	Q_a	Q_a^*
1847	1558	11083	1076	1262	1951	1656	42923	19738	13365
1871	1794	14969	8842	6002	1979	148	39581	19694	17972
1879	1260	7517	6650	121	1987	510	7949	7552	3677
1889	242	3779	1574	2231	1993	912	11959	8736	5546
1901	1722	3803	100	2394	1997	772	87869	72402	32194
1933	1058	23797	14251	7103	1997	1888	87869	87154	396
1933	1320	23197	11957	5213					

Irrespective of whether Fermat's Last Theorem is ever proved or disproved, the contents of the table given above constitute a permanent addition to our knowledge of cyclotomic fields, as its use will greatly simplify and facilitate the study of the units and ideals in such a field defined for any $l < 2000$.

[1] *Bull. Am. Math. Soc.*, **47**, 139–142 (1941).

[2] *Jr. für Math.*, **40**, 93–138 (1850); *Jr. Math.*, **16**, 454–498 (1851). An outline of the proof of this Theorem is given in the *Am. Math. Monthly*, **53**, 569–571 (1946). This last paper will be referred to as F.

[3] *Abhandl. Akad. Wiss., Berlin*, 41–74 (1857, 1858). See F, pp. 571–574 (1946). In F there are misprints in two places in the statement of (3). In the relation (17a), p. 568, the summation sign on the right should be a multiplication sign; and the quantity r^{-2in} should be an exponent of $e(\zeta^{rt})$. Also, in the right-hand member of the equation at the top of p. 572, the addition sign should be a multiplication sign.

[4] *Trans. Am. Math. Soc.*, **31**, 631, 638 (1929). The proof for case (I) was given in *Bull. Am. Math. Soc.*, **40**, 118 (1934). Cf. F, pp. 574–575.

[5] The formula (5) was obtained by Mirimanoff, *Jr. für Math.*, **128**, 45–68 (1905), for the special case where $l - 1$ is divisible by 12, and by Elizabeth T. Stafford and H. S. Vandiver for l general, these PROCEEDINGS, **16**, 143 (1930), relation (9). The relation (6) was proved by Vandiver, *Duke Math. Jr.*, **3**, 570–574 (1937), relation (18). Formula (7) is due to Emma Lehmer, *Ann. Math.*, **39**, 354 (1938), relation (19). In (6) if there is no integral s satisfying the condition given in a summation, then we define the summation as zero.

[6] *Duke Math. Jr.*, **3** (4), 569–584 (1937); *Ibid.*, **5**, 418–427 (1939) and previous references there given.

[7] *Nyt Tidsskrift für Matematik* (Afdeling B), p. 82 (1915) (in Danish). An outline of his proof is given in the "Report on the Theory of Algebraic Numbers, II," *Natl. Research Council Bull. No.* **62**, p. 82 (1928).

[8] If the so-called second factor of the class number of $K(\zeta)$ (cf. F, pp. 567–568) is divisible by l, then at least one of the E_{ai}, $i = 1, 2, \ldots, s$ is the lth power of a unit in $K(\zeta)$. Cf. *Bull. Am. Math. Soc.*, **35**, 333–335 (1929). The procedure in the proof of our lemma yields various forms of this criterion which appear to be of value for theoretical purposes.

[9] *Ann. Acad. Sci. Fennicae, Series A, Helsinki, I, Mathematica-Physica*, **60**, 18 (1949). Inkeri's theorem referred to here includes another extension of Theorem II aside from the one mentioned.

GEODESIC FLOWS AND UNITARY REPRESENTATIONS

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Let S be a complete surface of constant negative curvature. It is well known and readily verified that the geodesic flow on S can be described as follows. Let G be the group of all real 2×2 matrices of determinant 1 and Γ the fundamental group of

S acting in the upper half-plane, so that S is obtained with its Riemann metric from the upper half-plane with the non-Euclidean metric by identification modulo Γ. By means of the unique invariant measure on the coset space G/Γ form the Hilbert space $H = L_2(G/\Gamma)$ of complex valued square integrable functions on G/Γ. Let h denote the matrix $\begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}$ and $g_t = \exp(t \cdot h)$. Group translation defines a unitary representation U of G in H; hence in particular $U(g_t)$ is a 1-parameter group of unitary operators in H. This is the geodesic flow of S. Now let H_0 be the subspace of g_t-invariant elements x of H, $U(g_t)x = x$. Let $U(h)$ be the skew-adjoint operator for which $\exp tU(h) = U(\exp th)$. Then H_0 is in the domain D of $U(h)$ and $x \in H_0$ if and only if $x \in D$ and $U(h)x = 0$. Consider the ergodic parts obtained from the differentiable manifold G/Γ under the action of the 1-parameter group $\{g_t\}$. They are known[1] to be closed sets. And by considering the space obtained by identifying points belonging to the same ergodic part, it is easily proved that there exists a dense linear subspace H_1 of H_0 whose elements are differentiable functions and such that their partial derivatives are still in $L_2(G/\Gamma)$. Hence if $e_+ = \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}$ and $e_- = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}$, then the corresponding skew-adjoint operators $U(e_+)$ and $U(e_-)$ may be applied to all elements of H_1. Therefore the relations $[h, e_+] = 2e_+$ and $[h, e_-] = -2e_-$ imply that

$$U(h)U(e_\pm)x - U(e_\pm)U(h)x = \pm 2U(e_\pm)x \tag{1}$$

have meaning for $x \in H_1$ and in particular that $U(e_\pm)x$ are again in the domain of $U(h)$. Therefore

$$U(h)\{U(e_\pm)x\} = \pm 2U(e_\pm)x \text{ for } x \in H_1 \tag{2}$$

so that $U(e_+)x$ and $U(e_-)x$ are in the domain of $U(h)$ and are eigenvectors of $U(h)$ with real eigenvalues, whenever $x \in H_1$. But since $U(h)$ is skew-adjoint, this is impossible unless $U(e_+)x = U(e_-)x = 0$. This proves that $x \in H_1$ implies that $U(e_+)x = U(e_-)x = 0$. But since h, e_+, and e_- span the Lie algebra of G, this proves that $x \in H_1$ implies $U(g)x = x$ for all $g \in G$. Thus x must be a constant on G/Γ. Now assume that the total measure of G/Γ is finite (this is equivalent to the non-Euclidean area of S being finite). Then the above proves that $H_0 = H_1$ consists exactly of the constants, i.e., that the flow $U(g_t)$ is ergodic. *This proves the theorem of Hedlund and Hopf on the ergodicity of geodesic flows on complete surfaces of constant negative curvature and finite non-Euclidean area.*

It should be mentioned that a group-theoretic proof of this has recently been published by I. M. Gelfand and S. V. Formin.[2] Their method yields some detailed information about the spectrum of the flow, but uses the explicit knowledge of the irreducible representations of G and the fact that H is a direct integral of irreducible representation spaces. On the other hand, our method can be readily generalized in several ways. In essentially the same way as above one proves that the only eigenvectors of $U(h)$ are the constants. Also the above simple argument works in higher dimensions as follows. Let G be a Lie group and assume that its Lie algebra is generated by elements e_a and one element h which satisfy

$$[h, e_a] = ae_a,$$

where the "roots" a are non-zero real numbers. Then one proves that *if H is any unitary representation space of G and if $U(h)x = \lambda x$ for $x \in H$, then $U(g)x = x$ for all $g \in G$.* This can be applied to the large class of Riemann manifolds M which are obtained from E. Cartan's globally symmetric Riemann spaces of negative curvature by identification modulo a properly discontinuous group of motions.[7] This contains the higher dimensional cases treated by E. Hopf[3] and I. M. Gelfand and S. V. Fomin.[2] Details of this will be published elsewhere.

The above results on the ergodicity of certain double cosets should be compared with the following criterion which gives rather different sufficient conditions for the ergodicity of double cosets and can also be applied very easily to such groups as for instance the non-compact classical groups.

Let G be a locally compact topological group which has no non-constant finite dimensional continuous unitary representations. Let K be a closed subgroup of G such that the coset space G/K has an invariant measure m and such that $m(G/K)$ is finite. Then the only measurable functions $f(g)$ which satisfy (almost everywhere) $f(hgh') = f(g)$ for $g \in G$, h and $h' \in K$, are the constants.

Proof: Suppose there exists a measurable function $f(g) = f(hgh')$. Then one may take $f(g)$ to be bounded. Now consider the function $b(x, y) = f(xy^{-1})$. Clearly $b(hx, h'y) = f(hx(h'y)^{-1}) = f(xy^{-1}) = b(x, y)$. Thus $b(x, y)$ is a bounded measurable function on the Cartesian product $G/K \times G/K$. And therefore $m(G/H) < \infty$ implies $\int\int |b(x, y)|^2 dm(x)dm(y) < \infty$. Hence if $\varphi(y)$ varies arbitrarily over $L_2(G/K)$ then the equation

$$(B\varphi)(x) = \int_{G/K} b(x, y)\varphi(y)dm(y)$$

defines an operator B of the Hilbert-Schmidt class, acting on $L_2(G/K)$.

If $R(g)$ denotes for every $g \in G$ right-translation in $L_2(G/K)$ then

$$\begin{aligned}[BR(g)\varphi](y) &= \int b(x, y)\varphi(yg)dm(y) = \int b(x, yg^{-1})\varphi(y)dm(y) \\ &= \int f(x(yg^{-1})^{-1})\varphi(y)dm(y) = \int f(xgy^{-1})\varphi(y)dm(y) \\ &= \int b(xg, y)\varphi(y)dm(y) = [R(g)B\varphi](y).\end{aligned}$$

Thus $R(g)B = BR(g)$ for every $g \in G$. Therefore if λ is any eigenvalue of B, $\lambda \neq 0$, then the corresponding subspace of eigenvectors is a finite dimensional subspace of $L_2(G/K)$ which is invariant under every $R(g)$. Hence the restriction of $R(g)$ to this subspace determines a finite dimensional continuous unitary representation of G.

If for any eigenvalue $\lambda \neq 0$ of B this finite dimensional representation of G is the identity representation, then each eigenvector corresponding to it would have to be a constant function on $L_2(G/K)$. Hence if $f(g)$ is not constant then one obtains in this manner a non-trivial finite dimensional continuous unitary representation of G. This contradiction completes the proof.

The above should be contrasted with a result of C. L. Siegel, Theorem 1[4] according to which (under assumptions different from the above) the double cosets are discontinuous, i.e., behave in a very different manner. The above criterion can be applied, for example, to the case where G is the group of all real 2×2 matrices of determinant one, and K any discrete subgroup of G with $m(G/K) < \infty$. Thus K can, for example, be the modular group or more generally again the fundamental group of any Riemann surface, whose total hyperbolic area is finite. These ex-

amples can be generalized to higher dimensions by taking for G any semi-simple Lie group with no compact simple factors and for K, for example, any of the discrete subgroups with $m(G/K) < \infty$ which have been studied by C. L. Siegel.[5] The behavior of double cosets is also of importance in the theory of induced representations[6] and the last criterion above implies that this theory does not yet apply to the cases G/K just described.

[1] von Neumann, J., "Zur Operatorenmethode in der Klassischen Mechanik," *Ann. Math.*, **33**, Satz 2, 617 (1932).

[2] Gelfand, I. M., and Fomin, S. V., "Geodesic Flows on Manifolds of Constant Negative Curvature," *Uspehi Matem. Nauk*, **7**, 118–137 (1952).

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ORAL ADMINISTRATION OF POLIOMYELITIS VIRUS TO MAN AND APE—A COMPARATIVE STUDY

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The assumption that alimentary infection plays an important role in the pathogenesis of human poliomyelitis has led scientists in the past two decades to investigate the mechanism of the infectious process following oral administration of the virus to cynomolgus monkeys[1] and chimpanzees.[2] Because of the disparity in the cost of the two species of animals, a much larger number of cynomolgus monkeys than of chimpanzees has been used in the experimental investigations. Although the results of these studies seemed to indicate that the chimpanzee is a more susceptible experimental host than the cynomolgus monkey because of a higher rate of alimentary infection after oral ingestion of poliomyelitis virus, it must be borne in mind that the groups compared were of unequal size.[3, 4] Moreover, it has been impossible until now to apply the results obtained either in chimpanzees or in cynomolgus monkeys to the field of human poliomyelitis because of the lack of data correlating quantitative results of indirect studies in human beings with those conducted by the direct method of oral administration of the virus to the animal species.

Recently, however, a living attenuated poliomyelitis virus, the TN strain, was orally administered to two groups of human beings who were subjected to extensive study concerning the occurrence rate of alimentary infection, the presence of virus

in blood, and the immune response to infection.[5, 6] The same strain of virus and, in some instances, the same pool of infectious material, was fed to chimpanzees and cynomolgus monkeys in several experiments.[7] The purpose of the present short account is to present data on the comparative susceptibility of man, chimpanzee, and cynomolgus monkey* to the oral administration of the same strain of virus. Since some of the details of the experimental investigation included in the present paper have already been reported[5, 6] or will be published elsewhere,[7] only the essential data will be discussed here.

As indicated in table 1, seven virus pools were used as inocula. With one exception, all were of cotton-rat origin. Pool YHP N-63 was made from the brain and spinal cords of baby hamsters. In all cases a 20 per cent suspension of central nervous system tissue was used. Although all virus pools with the exception of

TABLE 1

RESULTS OF ORAL ADMINISTRATION OF TN STRAIN TO THREE SPECIES OF PRIMATES[a]

POOL NO.	SPECIES	DOSE OF VIRUS (ML.)	TOTAL NUMBER FED	NUMBER EXCRETING VIRUS	NUMBER SHOWING ANTIBODIES	RANGE OF ANTIBODY TITER
16	Man	1, 5, or 10	9	7	9	1:20–1:500
	Chimpanzee	10	2	1	2	1:85–1:95
21		10	2	1	2	1:60–1:700
23	Man	10	5	3	5	1:32–1:2500
24		5 or 10	8	5	8	1:10–1:600
F_1	Chimpanzee	2 × 10	3	1	3	1:7 –1:300
	Man	5	54	31	54	1:15–1:500
31	Chimpanzee	10	4	0	4	1:2 –1:35
	Cynomolgus	3 × 2	11	0	0	...
	Cynomolgus	2 × 6	5	0	0	...
YHP N-63	Cynomolgus	3 × 2	5	1	2	1:2
Grand Total	Man	...	78	47	78	...
	Chimpanzee	...	9	2	9	...
	Cynomolgus	...	21	1	2	...

[a] In no instance included in this table were signs of illness noted.

Pool 31 in one trial were administered in multiple alimentary inoculations, the data presented refer to only the first administration of the virus. (Chimpanzees receiving Pool F_1 were fed 10 ml. three days apart.)

In all experiments with all species of animals, the technique for detection of the virus in stool suspensions consisted of collection of stools at three-day intervals from the 3rd to the 24th day after virus ingestion, preparation of fecal suspension, and inoculation of the suspension intracerebrally into mice.[5]

Neutralization tests were performed in mice against the Type II strain[5, 6] and all sera were found to be devoid of neutralizing antibodies prior to ingestion of virus. Sera were again tested for presence of antibodies 30 days after administration of the virus (last column in the table).

Detailed statistical analysis of the results cannot be made since the species groups were of unequal size, man representing the largest group and chimpanzee

the smallest. Moreover, in many cases different pools of virus were fed to different species. Nevertheless, certain conclusions may be drawn as to the comparative susceptibility of the three species to the virus ingested orally. Since Pool 31 was fed to man, chimpanzee, and cynomolgus monkey within the same time period, the results obtained with this inoculum are perhaps of greatest significance. It will be noticed that out of 54 human beings fed with this pool, 31 became intestinal carriers and all 54 developed homologous antibodies, which ranged in titer from 1:15 to 1:1500. None of the four chimpanzees fed with the same pool were found to excrete virus, and though all four developed antibodies the titers ranged much below those observed in man. In marked contrast to these results, none of the 16 cynomolgus monkeys became intestinal carriers and none developed antibodies following feeding of 2 ml. of virus on three consecutive days or 6 ml. on two days.

These data become more significant when the grand total results are examined. The high susceptibility of man to alimentary infection with poliomyelitis virus is illustrated by the finding that a large number of individuals became intestinal carriers and all showed an overwhelming response in antibody production. The susceptibility of the chimpanzee may be distinguished from that of man by the lower rate of intestinal carriage. The immunity response measured by the development of neutralizing antibodies, though observed in all chimpanzees, was much less intense than in man. In contrast to men and chimpanzees, cynomolgus monkeys were apparently not susceptible to TN virus ingested orally.

Although broad generalizations cannot be drawn from the present results, obtained with a laboratory-adapted, attenuated strain of virus, it appears that this comparative study may serve as a guide for future investigators who may attempt to apply data obtained in animals to the field of human poliomyelitis. It is quite obvious that the usefulness of the cynomolgus monkey is limited, whereas the data obtained in chimpanzees bear more directly on general problems concerning the pathogenesis of the disease in human beings. It is also clear that for certain questions the crucial answers may have to be sought in man himself since data obtained in animals may be inadequate.

* The authors are greatly indebted to Dr. Albert B. Sabin for his suggestion to include cynomolgus monkeys in the feeding experiments and for advice on the procedures used by him in attempts to establish oral infection with poliomyelitis virus in a cynomolgus monkey.

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ENVIRONMENTAL RELATIONS OF MODIFICATION COMPOSITIONS OF CERTAIN CARBONATE SECRETING MARINE INVERTEBRATES

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Studies by numerous investigators, both incidental and direct, on the modification composition of skeletal carbonate in recent marine organisms have established that the stable modification calcite and the metastable aragonite constitute the commonly secreted constituents, singly or in combination.[1–6] Mostly going hand-in-hand with studies of skeletal micro-architecture, the purpose of the investigations has been to determine the distributional representation of the two modifications through the spectrum of carbonate synthesis with reference to the successive levels of organization. Undertaken for obvious reasons along taxonomic lines, random selection of species secured from biologic collections served in general for the analyses. The locations of specimen derivation and relation to ecologic aspects were in almost all instances of no concern, the compositional determinations serving primarily to add to the taxonomic diagnosis of the species examined. Data accumulated over a period of time on the mineralogic composition of random selected species within most classes from the family level up, in some cases as high as the phyllum level, as in the echinodermata, showed mostly identical modification composition. From this the concept evolved that with the exception of the two molluscan classes, the gastropods and pelecypods, comparatively uniform modification synthesis is the rule, the skeletons within taxonomically deformed limits consisting either entirely of calcite or aragonite. In the two molluscan classes, however, considerable complexity is involved. Calcite and aragonite occur there not only singly in skeletons as in the other classes, but both minerals may partake in the composition of single shells. In such instances the two modifications form micro-architecturally separate elements. As far as the distribution is concerned, the modification composition was found to differ in certain families and in some instances noted between species within a genus.[3] It is perhaps for this reason that these two molluscan classes have been investigated more thoroughly from the statistical point of view than any others. By now there exist diagnoses of the modification composition for all known carbonate secreting groups, though to judge from the literature controversies are in evidence in a few instances. They involve the entire phyllum bryozoa,[2, 3, 7, 8, 9] the serpulidae[2, 8, 9, 10, 11] among the polychaete worms, and recently certain molluscan species.[3, 6] Analysis of the reasons for these particular uncertainties show that, frequently, later determinations of random selected representatives of these groups differed from those made earlier, leading to questioning of the accuracy of determinations of one or another investigator. This is perhaps best illustrated by Stolkowski's[6] recent disagreement as to the composi-

tion of an individual of the same species of *Haliotis* determined by him to consist entirely of aragonite, as contrasted to the earlier diagnosis by Bøggild[3] stating that a volumetrically small calcitic layer is intercalated between the well-developed aragonitic ones. The basic philosophy involved, though not stated in these words, seems to pertain to the generally held concept that the modification synthesis products on the species level, and in most categories for the entire groups diagnosed, are constant. Thus, the mineralogic composition was inferred to be rigidly, that is genetically fixed. This perhaps explains the reason why the locations of respective sample derivations remained beyond consideration in the evaluation of the differences in modification determinations. This very aspect would involve the possibility of ecologic controls. This question was actually considered by Bøggild.[3]

TABLE I

SERPULIDAE WORM TUBES

LOCATION	LATITUDE	T. °C., MEAN AND RANGE	ARAGONITE, %
Malmøya, Oslo Fiord, Norway (3)	59°40′ N.	10.4 0.22–22.03	62
St. Paul Is., Pribilofs (1)	57°20′ N.	4.0 0.24–9.94	0
Southwestern coast Amchitka, Aleutians (2)	51°37′ N.	5.0 2.2°–8.7	0, 0, 0, 0, 0, 0, 0, 15, 22
Gloucester Point, Va. (6)	37°15′ N.	22.9 14.7–27.3	59, 64
(8)		24.5 20.0–27.3	53, 56
(9)		25.1 19.9–28.1	74, 84
Okinoshima, Honshu, Japan (4)	35° N.	18 12.1–24.2	28, 39, 41, 43, 50, 51
La Jolla, Calif. (5)	32°50′ N.	17 14.0–20.77	18, 29, 53, 54
Bermuda: (7) inshore waters	30°20′ N.	23 16–30	58, 63, 66, 68, 70, 76, 76, 77, 80, 80, 85, 86, 86, 89, 96, 96
Mangrove Lake			98, 98
Ngerikui, Passage of Koror Island, Palau (10)	7°19′ N.	28.0 27.5–29.5	90, 96, 96

His conclusion however, based on admittedly limited data, was that ecologic variables were not effective. Since then, no further consideration has been given to the possibility of ecologic relations to the modification composition in carbonate skeletons.

It is the purpose of the following presentation to show that within certain classes the mineralogy of skeletal materials is environment-dependent. The survey on which this study is based pertains principally to the analysis of one of the groups open to question in the literature, the serpulidae, and considers examples similarly found by the writer among the gastropods and pelecypods only as far as they contribute to the elucidation of the problem.

Modification compositions in the study were determined on powdered smear slide preparations by means of a Phillips x-ray spectrometer with attached Brown Recorder. Whenever both calcite and aragonite were found to be present, their relative amounts were found using a calibration curve derived from synthetic mixtures and established by K. E. Chave and further improved by L. Silver and H. Fahy. The accuracy of the measurements is $\pm 10\%$. The uncertainty in the measurements of the amount of mineral decreases if the ratio of the two forms is less than 1/10. Because of the small size of most serpulidae worm tubes examined, determinations are largely based on composites of a number of them to assure large enough samples. In view of the composite nature of most of these samples and the limited accuracy of the mineralogical determinations where both modifications are involved, the significance of the serpulidae data must rest entirely on trends rather than the percentage determinations *per se*.

To assure proper comparison between modification composition and ecologic conditions, in particular environmental temperatures and salinities, the survey is based on recently-collected specimen series either from localities where the yearly climatic amplitude and salinity ranges of the inhabiting waters were available, or at least from locations nearby to hydrographic stations where there were no indications of marked micro-environmental deviations. In view of the survey nature of the investigation the samples for the study were selected from widely distant locations extending from high to low latitudes. Specific identifications for most of the forms employed in the study are lacking.

Table 1 shows the modification composition of the serpulidae worm tubes analyzed, arranged in the order of their latitudinal derivations from low to high latitudes. The modification compositions determined range from 100% calcite through varying percentages of calcite and aragonite to 98% aragonite. In general the modification composition of the serpulidae worm tubes is shown not only to vary from one geographic location to another, but also within local populations. As illustrated by the Bermuda samples, which encompass the largest number of analyses from any single locality, the range in compositional variation extends far beyond the limits of error of the method involved. Only the Aleutian samples constitute a possible exception. Two of the initial runs out of a total of seven showed small amounts of aragonite. Since subsequently run samples gave 100% calcite throughout, it is suspected that we are dealing in these early identifications with admixtures of small amounts of aragonitic shell substrates from which the worm tubes had been removed. If so, the Amchitka serpulidae would constitute a decided exception to constancy in modification composition. Analysis of the overall variability shows that even when viewed on as general a basis as latitudinal distribution that entirely calcitic tubes are confined to the high latitudes, the subarctic, while mixtures with more than 85% aragonite are derivatives from the subtropics and tropics. The modification compositional ranges for the samples of each locality were therefore plotted against yearly mean temperatures of their inhabiting waters. The results (Fig. 1), show that at least partial temperature-controlled modification synthesis is involved. Viewed within the framework of the gross temperature effect on the modification synthesis products for this group, the observed variability shown to extend down to the population level of single localities is not only compatible but should exist once the consideration is extended to the ranges

of the yearly amplitude of the inhabiting waters. If the synthesis of the modification types or relative amounts in the tube formations are in this group in some way and within certain limits temperature dependant, the mean averages of individuals or composite samples should vary according to the time interval over which the tubes formed, the yearly temperature range, and the cumulative response in volume secretion per temperature integral thereof. Hence in waters with a wide yearly amplitude, such as at Bermuda, where temperatures range from 16 to 30°C. and where we have evidence that serpulidae worms grow, as well as spawn, in winter and summer, variations in modification composition over the range exhibited are to be expected. The Bermuda sample series from the inshore waters alone is most suitable to explore further this inference. This series consists of the largest number of

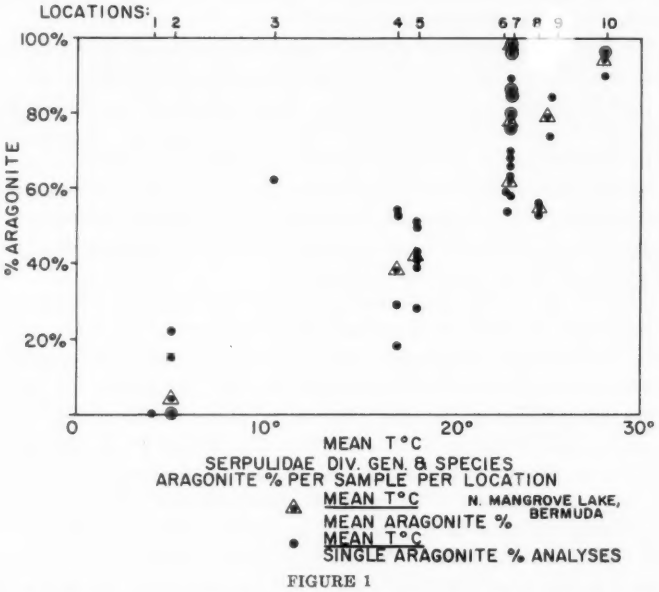

FIGURE 1

Closed dots represent single aragonite analyses; circled dots represent the mean value for two or more aragonite analyses per species. Dots surrounded by triangles represent the average of all the analyses for all species considered in a single location. The triangular point located on the graph at 60% aragonite and 23°C should be deleted.

samples analyzed, hence statistically gives greater assurance of covering more accurately the range of variations in aragonite percentages involved.

There is another aspect which seems equally critical for the selection. If the temperature environment does enter into the controls of skeletal modification synthesis, other environmental factors might also be involved, though perhaps to a lesser degree, and be responsible for some of the more marked deviations from the growth trend, noticeable in figure 1, which cannot be attributed to error of the determination method. A factor to be considered is salinity since it is known to affect skeletal morphology. In the Bermuda inshore waters salinity is virtually

constant the year around, at the most fluctuating 1 per mille from the norm of 35 per mille, and hence can be eliminated from the consideration. Although the variables which may enter into the analysis of the Bermuda population samples are thus reduced, the information available for examining the relations of the aragonite percentages to temperatures of synthesis is far from satisfactory. In only one case, which involves one of the two lowest aragonite percentages determined, is there comparatively more precise information on the growth period available. The sample, analyzing 63% aragonite, represents a composite of several small tubes grown during the intermolt period on the carapace of an individual of *Panulirus argus*, kept under observation in a tank at the Biological Station, with daily temperature records. Although there is no assurance that the beginning of growth of the serpulidae worm tubes coincided with that of the intermolt period, the fact that the temperature range covered by the latter falls between 16 to 22.9°C., the coldest part of the year, and that the aragonite percentage of the worm tubes grown somewhere within this range is the second lowest analyzed, forms a strong argument in favor of the interpretation offered. For the balance of samples only the temperatures of the collecting dates are available. Secured over a period of rising spring and summer temperatures increasing aragonite ratios should be in evidence when grouping the samples in the order of successively higher temperatures of their collecting dates. Admittedly this constitutes a rather crude approximation, particularly since the tubes at the time of collecting had not been examined to see whether they were alive, that is, were growing in the immediately preceding time-temperature interval. As shown in table 2, there is in their successive scatter ranges a gross in-

TABLE 2

LOCATION	T. °C. AT TIME OF COLLECTING	ARAGONITE, %		
		MIN.	MAX.	MEAN
Harrington Sound	25	58	77	67
Cock Rocks	27	68	80	75
Emily Bay	27	66	96	77
Harrington Sound	29	80	89	85

crease in aragonite percentages corresponding to increasing temperatures of the date of collection, minimum values and range means in particular exhibiting definite alignment. The deviation in the two sample series taken at the same temperature from Emily Bay, an inshore bay, and of Cock Rocks, facing the open ocean on the south side of the islands, could well be attributed in part to their respective microenvironmental climates and to differences in cumulative growth periods of the tubes analyzed. It would thus seem that within the limits of the means of comparison the Bermuda sample series indicates that temperature control of the skeletal modification composition in this biotic group extends clear down to the local population level, hence in principle corroborates the gross trend relations. The three sets of samples from Gloucester, Virginia, show a lesser degree of correlation than the Bermuda ones (figure 1), despite the fact that they were derived from test stakes for which the length of submergence and corresponding temperature and salinity data were made available by Dr. Sheltema. The aragonite percentages of the two extremes in temperature range derivation, as far as the period of submergence of their respective substrates is concerned, follow the generally indicated trend, but the intermediate one very close to the highest temperature derived sample

does not. Of the possible reasons to account for the phenomena, partial growth cover of the submergence period of the stake seems reasonable, as the worm tubes here were considerably smaller and more slender than those from the two other ones. If so, their growth period had to be confined to temperatures in the low twenties. In the absence of information on whether the *Hydroides* individuals were alive at the time of the stake recovery this interpretation cannot be verified.

Reference has been made earlier to deviations from the growth trend which decidedly fall far beyond the limits of error of the method involved. Specifically these pertain to the single sample from Malmøya in Oslo fjord, Norway, and the Bermuda samples from Mangrove Lake. The aspect in common to both is that their respective aragonite percentages lie above the upper limits suggested by the scatter band width in the gross trend relations inferred. In both cases the samples were derived from environments where the salinity is either low, as is the case of Malmøya, or in the case of Mangrove Lake markedly fluctuated over a considerable range during the year, a point in common only with the samples of Gloucester, Virginia, with ranges extending down to as low as 18 per mille. By contrast the salinities of the habitats of all other samples lie above 30 per mille and fluctuate only over a narrow range if at all. The inference might be drawn that salinity may in these two instances account for the deviations, and if so would indicate that low salinities tend to raise the aragonite synthesis above that determined by environmental temperatures alone. However, there is no obvious correlation in the three Gloucester samples. As far as the incidence of an observed temperature effect is concerned, a preliminary survey of other carbonate secreting organisms has shown that it extends outsi[illegible]he serpulidae to the spirorbidae among the polychaete worms, and also emb[illegible] *Modiolus, Mytilus, Pedalion, Pteria, Pinctada, Pinna, Pecten, Li*[illegible]ng the pelecypods, and the genera *Patella, Haliotis, Fissurell*[illegible]*ittorina* among the gastropods. The mode of temperature respo[illegible]orbis group seems to differ from that in the case of the serpulidae in t[illegible]ubes from mean environmental temperatures of 18°C. upward are entirely composed of aragonite, and hence seem to show responses in modification composition only in the lower temperature ranges.

In the mollusca the mineralogic composition and their temperature responses, where observed, differ markedly from genus to genus and also within genera from species to species. An exploratory study of this relationship in the mollusca cited permits evaluation of certain aspects which could not be presented in the case of the serpulidae—for example, the variations of the modification compositions within the population of a single species. In the case of the serpulidae the entire yearly temperature range has to be considered, since members of individuals which could have grown at any time had to be used for single analyses. In the case of *Mytilus edulis* from Ocean City, Maryland, presented hereafter, the analyses were made on individuals grown over a short period, within a smaller specified temperature range. The specimens were derived from test stakes submerged over a period of 30 days during which the temperature increased from 17.1 to 23.2°C. Selecting a growth series of seven individuals representative of the entire size range, the analyses revealed a range in aragonite ratios for the shells from 35 to 69%. Assuming the weight of a given shell to correspond to age, with due regard given to differential weight increases in age selected population segments, and plotting the weights of

individual shells against their respective aragonite percentages, a trend of progressive decrease in percentages with increasing weight is observed (Fig. 2). Since larger shells imply correspondingly longer growth periods and thus include more of the colder initial temperatures characteristic of the earlier part of the 30-day period, the larger shells should then include more calcite, and thus have a lower aragonite-calcite ratio. Thus the inference of the mineralogic-temperature relationship shown by the Serpulidae is confirmed by the data for the *Mytilus* example. Further if the mean temperatures of the localities for the Serpulidae are plotted against the mean aragonite content of all samples of a given locality, the curve shown in figure 1 is obtained. Since it is impossible to specify the correct temperature ranges for any one sample, and since it is possible that the serpulidae in a specific locality, such as Bermuda, will grow throughout the year, a plot of the mean mineralogic compositions against the mean temperatures should convey a truer relationship. It is

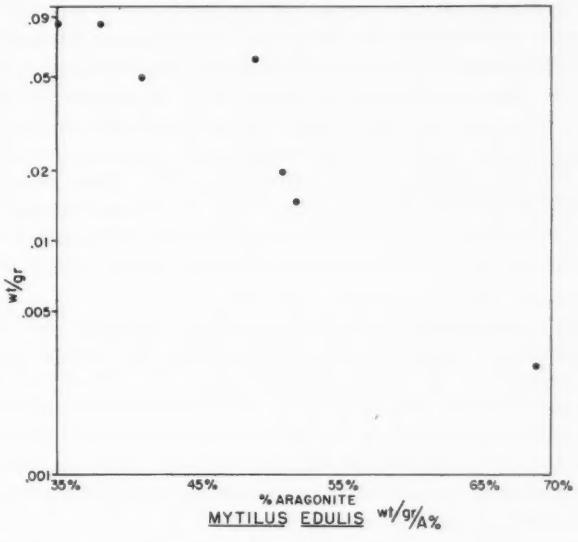

FIGURE 2

perhaps worth noting that the point most divergent from a linear relationship includes only one analysis (Malmøya) and thus could embody a growth period of large uncertainty as far as the temperature range is concerned, which in this case is from 0.22–23.03°C.

Another aspect which had not been considered in the analyses of the serpulidae data pertains to the comparative secretion behavior in modification synthesis products of various species. The existence of a species effect is demonstrated by the Mytilidae. *Smaragdensis* from the China Coast and the Philippines and *perna* from Ilha Grande, Brazil, occupy the tropical temperature niche and were composed of 100% aragonite. If there were no species effect, if the above species behaved in their modification synthesis analogous to *Mytilus edulis*, previously discussed, then the Brazilian species, *perna*, living in a locality with low enough temperatures during

part of the year (18.9–27.8°C.) to overlap with those of *edulis* at Ocean City, Maryland (17.1–23.2°C.) should contain some calcite in its skeletal makeup. Since the limited data indicate this is not true a species differentiation in responses is inferred. Investigations of the cross-sectional temperature records of some recent mollusc shells by means of the O^{18}/O^{16} ratio have shown that the temperature niche of shell deposition for a given species may not coincide with its temperature tolerance. In *Chama macerophilla*, an extreme case, shell deposition at Bermuda was shown to occur only at the elevated temperatures.[12] The species-determined differences in modification depositional responses noted between *Mytilus edulis* and *Mytilus perna* may perhaps be attributed to a similar phenomenon, offsetting the temperature threshold limits of their respective shell secretionary ranges, in that *perna* does not lay down shell in the overlapping temperatures, that is, below 23°C. This distinct possibility points to one of the possible controls of the observed differences in species-determined modification synthesis products.

However, in this particular example the species do not occupy overlapping geographic ranges. An example illustrating the most extreme differentiation in two gastropod species, occupying in overlapping depth ranges the inter-tidal zone on the Pacific coast, is *Littorina scutulata* and *L. planaxis*. Populations of the two species secured alive *in situ* at the same locality at La Jolla, California, analyzed 100% aragonite for *planaxis*, while those of *scutulata* are composed of both calcite and aragonite, with aragonite ratios ranging from 21 to 45%. Thus we have an example of two species essentially occupying the same environmental niche, one being environment-independent as far as its ecologic valence with reference to the local climatic conditions, the other temperature-dependent in its modification synthesis products.

While a temperature-modification compositional selection has been shown to exist in the groups under consideration, the possibility of other less marked ecologic effects superimposed on the former cannot be ignored. Their evaluation, if they exist, is not possible with the data at hand. It seems tempting, as indicated above, to interpret those deviations from the gross trend in the Serpulidae and Mytilidae with apparently high aragonite percentages from the Baltic Sea, as the result of other effects, in particular of lowered or fluctuating salinities superimposed on the temperature effect.

The data presented call clearly for an amending of the generalization that biochemical carbonate synthesis in skeletal form with reference to modification composition is genetically fixed, at least at the species level. While this appears to be the case in most of the phyla of carbonate secreting forms, evidence has been presented to show that exceptions do exist. These involve at present components of representatives within two phyla of higher levels of organization, the serpulidae and spirorbidae among the polychaete worms, and numerous genera of certain orders within the two molluscan classes gastropods and pelecypods. Within these the skeletal modification composition is dependent in numerous species upon factors of the environmental framework, definitely upon temperature. The temperature effect is expressed by the increase in aragonite over calcite with elevation in temperatures. Species-determined responses, differing in the modes of behavior in modification synthesis, are shown to be effective in the molluscan examples. Hence there is evidence that ecology, in the form of temperature, directly or indirectly

influences biochemical carbonate secretion in the skeletal modification synthesis by governing its composition, which is also potentially subject to the modifying effects of species controls.

One obvious implication of this modified concept of environmentally-affected aragonite ratios concerns the chemistry of the major trace element strontium in skeletal carbonate. Noll[13] has shown that the lattice uptake of this element is governed by the modification type of the carbonate involved. It is comparatively small, up to 0.14% in the stable modification calcite; in the metastable phase aragonite it can be maximally 4.69%, calculated as SrO.[13] In skeletal carbonates Odum[14] and Kulp, *et al*,[15] to cite the most recent references, have stated that concentration levels of strontium differ not only according to the carbonate modifications involved, but also as a function of strontium concentration in the aqueous medium, and are sensitive to biologic differentiation within the same mineralogic modification. However, as far as other environmental factors are concerned, they imply that the strontium content is independent of temperature. Partially correct in principle the statement requires revision as far as its generalization is concerned. Within the groups shown here to be at least temperature-dependent an increase in strontium concentrations should be in evidence as the result of the increase in aragonite. Figure 3 shows the relation of strontium concentration, calculated as strontium carbonate, in the serpulidae worm tubes to corresponding aragonite percentages. An increase in strontium carbonate with increase in the aragonite percentages is clearly in evidence. This obviously adds another complicating factor to the many already in evidence in tracing the history of the strontium cycle through geologic time, as it involves consideration of the distinct possibility of evolutionary changes in skeletal carbonate modifications and ecologic responses, two aspects intriguing in themselves from the biologic point of view.

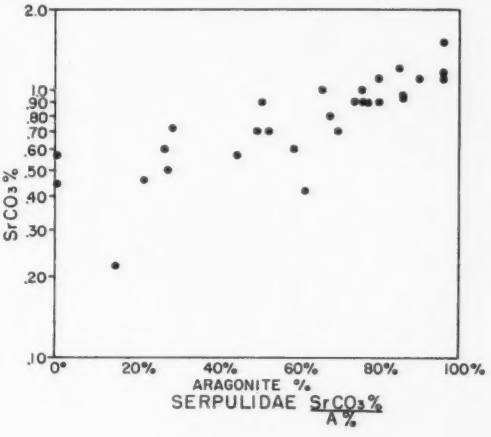

FIGURE 3

* This investigation was supported in part by grants from the Shell Oil and Jet Oil Companies and the California Research Corporation.

† Contribution No. 652.

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